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META-ANALYSIS

Expression of epithelial cellular adhesion molecule in gastric cancer: A meta-analysis

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Abstract

AIM: To obtain an accurate evaluation of the association between high expression of epithelial cellular adhesion molecule (EpCAM) and gastric cancer (GC) risk.

METHODS: Studies that had examined the association between high expression of EpCAM and GC risk were identified by searching electronic databases PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature database. Risk ratios (RRs) together with their 95%CIs were used to assess the association between high expression of EpCAM and GC risk. We selected eligible studies based on inclusion criteria. RevMan 5.3 software was used to calculate the pooled values.

RESULTS: A total of 14 studies were included in this meta-analysis. EpCAM-positive cases were significantly associated with tumor size (RR: 1.68, 95%CI: 1.47-1.91, $P < 0.00001$ fixed-effect), depth of invasion (RR: 1.37, 95%CI: 1.11-1.68, $P = 0.003$ random-effect), TNM stage (RR: 2.02, 95%CI: 1.35-3.02, $P = 0.0007$ random-effect), tumor location (RR: 0.80, 95%CI: 0.71-0.91, $P = 0.0007$ fixed-effect), histologic differentiation (RR: 1.23, 95%CI: 1.13-1.33, $P < 0.00001$ fixed-effect) and lymph node metastasis (RR: 1.89, 95%CI: 1.28-2.80, $P = 0.001$ random-effect). However, we did not observe any significant association between the presence of EpCAM with age, gender, distant metastasis, Borrmann type or Lauren classification. Additionally, EpCAM expression was not associated with the overall survival rate. The pooled HR of the overall effect was 1.39 (95%CI: 0.30-6.48, $P = 0.67$ random-effect).

CONCLUSION: Our meta-analysis indicates that EpCAM contributes to GC risk, which acts as a prognostic factor and a marker of poor outcome.

Key words: Epithelial cellular adhesion molecule; Gastric cancer; Prognosis; Progression; Meta-analysis

Core tip: This meta-analysis aimed to obtain an accurate evaluation of the association between high expression of epithelial cellular adhesion molecule (EpCAM) and gastric cancer (GC) risk. EpCAM-positive cases were significantly associated with tumor size, depth of invasion, TNM stage, tumor location, histologic differentiation and lymph node metastasis. EpCAM contributed to GC risk, and acted as a prognostic factor and a marker of poor outcome.

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INTRODUCTION

Although gastric cancer (GC) rates have decreased substantially in the past few decades, it remains the second most common cause of cancer-related death worldwide[1]. Patients with GC have a poor prognosis, especially those with advanced stage disease. The most common cause of this phenomenon is the advanced stage of most cases at the time of initial diagnosis. Additionally, tumor cell spread has occurred in some cases[1,2]. Currently, surgery is the primary treatment strategy for localized advanced GC, with an average 5-year survival rate of 20%-30%; however, for unresectable disease such as metastatic or recurrent GC, chemotherapy is regarded as a basic therapeutic approach[1].

The efficacy of current chemotherapeutic agents is still unsatisfactory and these agents with poor specificity have significant side effects. Consequently, multimodality therapy options are needed to improve the prognosis of GC. This necessitates finding new adjuvant therapeutic targets and prognostic markers for GC patients.

The epithelial cellular adhesion molecule (EpCAM) is a 37-42 KDa, 314-amino-acid type I transmembrane glycoprotein with two epidermal growth factor-like repeats in the external domain and two α-actin binding sites for actin cytoskeleton linkage in the intracellular domain[2]. The 9-exon gene TACSTD1, which has been mapped to chromosome 2p21, encodes it. EpCAM functions as a homotypic intracellular adhesion molecule. It is interconnected with E-cadherin during the process of epithelial cell adhesion[2,3].

EpCAM is expressed in most normal epithelial tissues on the basolateral membrane and overexpression of EpCAM has been detected in a variety of epithelial cancers[4]. EpCAM was found to be overexpressed in colon cancer tissues, breast cancer squamous cells, ovarian carcinomas and most human adenocarcinomas. Because its overexpression has effects on differentiation, cell proliferation, signaling and migration, EpCAM can be used as a marker to predict recurrence and metastasis of the tumor and influence survival of cancer patients[5].

Furthermore, EpCAM has been considered as a target antigen for a number of specific immunotherapies because of its frequent and high-level expression[6,7]. Catumaxomab, an EpCAM monoclonal antibody, has been used for the intraperitoneal treatment of malignant effusion in patients with EpCAM-positive cells since 2009. Catumaxomab also had a significant overall survival (OS) benefit in GC patients[8]. However, the role of EpCAM in GC is still unclear. Although several studies showed high expression of EpCAM in GC[6-10], which was related to cancer progression and survival prognosis, there is no comprehensive study on the correlation of EpCAM expression with survival prognosis or the effects of EpCAM expression on clinicopathologic characteristics in GC patients. Thus, this meta-analysis was conducted to determine the association between high expression of EpCAM and clinicopathological features and progression as well as prognosis of GC.

MATERIALS AND METHODS

Literature search strategy

We conducted a comprehensive literature search in PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature databases. There was no restriction on time period, sample size, population or languages. The search terms included "Stomach Neoplasms" OR "Gastric Neoplasms" OR "Stomach Cancer" OR "GC" OR "Stomach Carcinoma" OR "Gastric Carcinoma" AND "EpCAM" OR "epithelial cellular adhesion molecule". The search was limited to studies in humans. All eligible studies were retrieved and their references were scanned for other relevant studies. Two reviewers (Yi-Bin Xiao and Hong-Qing Xi) independently screened titles and abstracts of all citations. When multiple articles were reported on the same or overlapping data, we selected the study that investigated the most individuals or the most recent study.

Inclusion and exclusion criteria

Articles were considered if: (1) they provided information on GC verified by pathological examination; (2) they provided information on case control or cohort studies that evaluated the association between EpCAM expression and GC; (3) no preoperative chemotherapy and/or radiotherapy was administered to patients; (4) they had available data for estimating risk ratio (RR) (95%CI); and (5) the control population did not contain patients with malignant tumors.

Studies were excluded if they: (1) had no control population; (2) were duplicates of an earlier publication; (3) reported insufficient data; (4) had cell or animal experiments; and (5) were letters, reviews, case reports and conference abstracts without original data or articles

published in a book.

Data extraction

Two investigators (Yi-Bin Xiao and Hong-Qing Xi) reviewed all articles. Then the first investigator extracted the following information according to the prespecified selection criteria: (1) Publication details, including first author's name, year of publication and publication journal; (2) Characteristics of the studied population, including country, ethnicity, number of cases and controls; and (3) Number and characteristics of different clinical and pathologic parameters of both the gastric patients and their control group, including age, gender, tumor size, depth of invasion, TNM stage, tumor location, distant metastasis, Borrmann type, Lauren classification, histologic differentiation and lymph node metastasis.

Discrepancies between the two investigators were resolved through consensus discussion.

Quality assessment

The quality of the studies was assessed according to the Newcastle-Ottawa Scale (NOS) by two investigators (Yi-Bin Xiao and Hong-Qing Xi) independently. The scale includes three major classifications: Selection, comparability and outcome. A maximum score of 1 was graded for each item, except for comparability, where a score of 2 was allowed to be graded. Scores ranged from 0 (lowest) to 9 (highest) and studies that scored equal to or higher than 7 points were assigned as "high-quality" studies, whereas those with scores less than 7 were considered "low-quality" studies. Any disagreement was resolved through consensus discussion.

Statistical analysis

The association between EpCAM and GC risk was evaluated using hazard ratio (HR, 95%CIs) for time-to-event data (OS) and (RR, 95%CIs) for dichotomous data (various adverse events). Cochran's χ^2-based Q test and Higgins I^2 statistics were used to check heterogeneity among studies. I^2 lay between 0 and 10%, and a value of 0% meant no observed heterogeneity, with larger values indicating increasing heterogeneity. $P < 0.05$ or $I^2 > 50\%$ was considered statistically significant. A value of 0% indicated no observed heterogeneity, and larger values showed increasing heterogeneity, with 25% indicating low, 50% indicating moderate, and 75% indicating high heterogeneity (Higgins, Thompson, Deeks, and Altman, 2003).

We selected the fixed-effect model (the Mantel-Haenszel method) if there was no significant heterogeneity. Otherwise, we selected the random-effect model (the DerSimonian and Laird method) if heterogeneity existed and could not be explained or corrected. Begg's funnel plots were used to examine potential publication bias in this study. For the pooled analysis of the correlation between EpCAM expression and clinicopathological features, RRs and their 95%CIs were used to assess the effect. All the statistical tests were performed using RevMan5.3 (Cochrane collaboration, Oxford, United Kingdom) software. Kaplan-Meier curves were read using an Engauge Digitizer 4.1. $P < 0.05$ was considered statistically significant. HRs or RRs > 1 meant a worse prognosis for GC patients with EpCAM overexpression and were considered to be statistically significant if the 95%CI did not overlap 1. In addition, sensitivity analysis was conducted by sequential omission of individual studies to evaluate the stability of the results.

RESULTS

Literature search and characteristics

A flow diagram of the literature search is shown in Figure 1. The initial search yielded a total of 190 studies according to the search criteria. A total of 28 potential relevant studies were recruited into this meta-analysis. Of these studies, three were excluded because they contained overlapping data. Another 11 studies were excluded because they were unable to offer EpCAM-specific data for calculating HRs or RRs according to the described method. A total of 14 studies that met the inclusion and exclusion criteria were included. Three studies reported an association between EpCAM and the 5-year survival rate[7,11,12], and 13 studies[1-11,13,14] were chosen to demonstrate the connection between EpCAM expression and clinical features. As a result, we did not find any additional articles using a manual search of references cited in the published studies. The details of the articles are summarized in Tables 1 and 2.

Correlation of EpCAM with clinicopathological parameters

Thirteen studies reported correlations between EpCAM expression and some clinical characteristics of GC (including age, gender, tumor size, depth of invasion, TNM stage, tumor location, distant metastasis, Borrmann type, Lauren classification, histologic differentiation and lymph node metastasis). These were pooled to calculate the RRs.

In our study, the expression level of EpCAM was higher in samples of GC than in normal ones (pooled RR = 2.16, 95%CI: 1.54-3.03, $P < 0.00001$ random-effect) (Figure 2A). In addition, EpCAM expression was significantly associated with tumor size (pooled RR = 1.68, 95%CI: 1.47-1.91, $P < 0.00001$ fixed-effect) (Figure 2B), depth of invasion (pooled RR = 1.37, 95%CI: 1.11-1.68, $P = 0.003$ random-effect) (Figure 2C), TNM stage (pooled RR = 2.02, 95%CI: 1.35-3.02, $P = 0.0007$ random-effect) (Figure 2D), tumor location (pooled RR = 0.80, 95%CI: 0.71-0.91, $P = 0.0007$ fixed-effect) (Figure 2E), histologic differentiation (pooled RR: 1.23, 95%CI: 1.13-1.33, $P < 0.00001$ fixed-effect) (Figure 2F), and lymph node metastasis (pooled RR = 1.89, 95%CI: 1.28-2.80, $P = 0.001$ random-effect) (Figure 2G). However, EpCAM expression in GC was not associated with age (pooled RR = 1.12, 95%CI: 0.93-1.35, $P = 0.24$ fixed-effect), gender (pooled RR =

Table 1 Characteristics of included studies

First author	Country	Year	Ethnics	Age (< 50: ≥ 50)	No. of patients (male:female)	No. of patients (EpCAM+: EpCAM-)	Diagnosis of GC (Histo-, Patho-, NR)	Study quality (NOS)
Zhang *et al*	China	2011	Asian	11:31	24:18	34:8	Patho-	8
Sun *et al*	China	2010	Asian	31:29	48:12	46:14	Patho-	8
Fang *et al*	China	2010	Asian	27:31	39:19	46:12	Patho-	8
Lu *et al*	China	2011	Asian	43:48	70:21	84:7	Patho-	9
Yang *et al*	China	2014	Asian	33:39	57:15	48:24	Patho-	9
Peng *et al*	China	2011	Asian	20:11	18:13	21:10	Patho-	9
Yang *et al*	China	2012	Asian	33:62	66:29	56:39	Patho-	8
Zhang *et al*	China	2014	Asian	17:25	24:18	37:5	Patho-	7
Li *et al*	China	2012	Asian	NR	311:125	179:257	Patho-	7
Du *et al*	China	2009	Asian	26:74	61:39	74:26	Patho-	8
Went *et al*	Switzerland	2006	Caucasian	NR	311:117	NR	Patho-	7
Kroepil *et al*	Germany	2013	Caucasian	NR	NR	126:37	Patho-	8
Wang *et al*	China	2013	Asian	NR	428:173	247:354	NR	8
Songun *et al*	The Netherlands	2005	Caucasian	NR	NR	NR	Patho-	7

Histo-: Histology; Patho-: Pathology; NR: Not reported; NOS: Newcastle-Ottawa Scale classification; EpCAM: Epithelial cellular adhesion molecule.

Table 2 Raw data from each included study

First author	Tumor size (≤ 5 cm: > 5 cm)	Depth of invasio-n (T1-T2: T3-T4)	TNM stage (Ⅰ-Ⅱ:Ⅲ-Ⅳ)	Tumor location (upper:middle: lower)	Distant metastasis (yes: no)	Borrma-nn type (Ⅰ:Ⅱ:Ⅲ:Ⅳ)	Lauren classificatio-n (intestinal: diffuse: mixed)	Histologic differentiate-on (high: moderate: low)	Lymph node metastasis (N0: N1/2/3)
Zhang *et al*	NR[2]	NR	NR	NR	23:19			8:12:22	20:22
Sun *et al*	NR	11:49	NR	NR	NR	NR	NR	20:20:20	NR
Fang *et al*	NR	17:41	17:41	NR	18:40	NR	NR	11:17:30	15:43
Lu *et al*	41:50	19:72	34:57	41:25:25	NR	8:12:59:11	NR	3:24:64	31:60
Yang *et al*	45:27	35:37	35:37	NR	NR	NR	NR	NR	25:47
Peng *et al*	NR	19:12	19:12	12:13:6	NR	NR	NR	15:13:3	NR
Yang *et al*	NR	7:88	NR	29:26:40	NR	3:12:61:19	NR	6:19:70	29:66
Zhang *et al*	14:28	13:29	13:29	NR	NR	NR	NR	16:26:0	11:31
Li *et al*	256:180	166:270	194:242	55:163:218	61:375	NR	223:213:0	141:295	166:270
Du *et al*	NR	NR	NR	NR	NR	NR	91:19	25:42:33	50:50
Went *et al*	NR	42:372	NR	NR	25:445	NR	NR	NR	153:316
Kroepil *et al*	NR	107:56	NR	NR	9:154	NR	62:61:40	NR	41:122
Wang *et al*	350:251	221:380	262:339	84:223:294	91:510	NR	299:302	17:175:409	220:381
Songun *et al*[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR

[1]Article written by Songun *et al*. only provided OS data; [2]NR: Not reported.

0.97, 95%CI: 0.91-1.04, P = 0.37 fixed-effect), distant metastasis (pooled RR = 2.25, 95%CI: 0.77-6.61, P = 0.14, random-effect), Borrmann type (pooled RR = 1.03, 95%CI: 0.89-1.19, P = 0.70 fixed-effect), or Lauren classification (pooled RR = 1.64, 95%CI: 0.75-3.60, P = 0.21 random-effect).

Impact of EpCAM expression on OS in GC patients

Meta-analysis of the association between EpCAM expression and OS was determined in three studies. The pooled RR was analyzed using previously described methods. EpCAM expression was not associated with the OS rate. The pooled HR of the overall effect was 1.39 (95%CI: 0.30-6.48, P = 0.67) in the random-effect model (Figure 2H).

Assessment of publication bias

The funnel plot test recommended for meta-analyses was used to examine publication bias (Figure 3). We inspected its asymmetry visually and found that there was almost no potential for publication bias.

Sensitivity analysis

One included study was excluded at each time to investigate the influence of the individual data on the overall results. The pooled RR or HR estimates were recalculated for the remaining studies. The statistical significance of the overall results was not changed when any individual study was excluded, which indicates the reliability of our results.

DISCUSSION

In recent years, many cell adhesion molecules (CAMs) have proven to be responsible for tumorigenesis and metastasis[2,3]. The role of EpCAM is not only limited

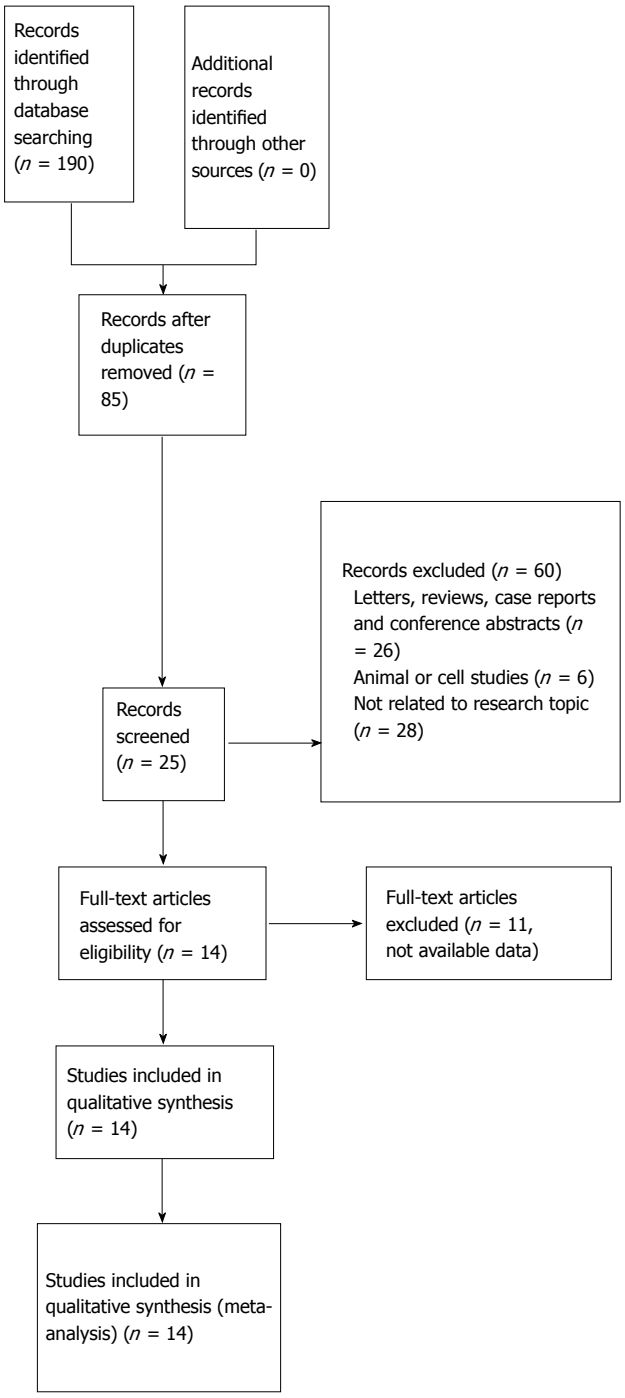


Figure 1 Study selection.

to cell adhesion but is also involved in other cellular processes including signaling, cell migration, proliferation and differentiation[15]. EpCAM is a potent signal transducer, which can use components of the Wnt pathway and is involved in the regulation of cell proliferation and cell cycle progression[5,13,16]. It is overexpressed in many solid cancers including esophageal, pancreatic, prostate and gastric[12,17], and it has recently been identified as a type of cancer stem cell marker[14,18,19].

Identification of a prognostic factor such as EpCAM is necessary for high-risk patients for whom specific therapy might be necessary[20,21]. However, conflicting data on the prognostic impact of EpCAM have been reported. Wenqi *et al*[22] reported that EpCAM was overexpressed in gastric cell lines and tumor tissues and downregulation of EpCAM resulted in a decrease in cell proliferation and suppressed tumor formation. In contrast, Songun *et al*[23] reported that 93% of 300 GC patients were EpCAM-positive and the loss of EpCAM expression indicated tumor aggression, especially in patients with stage Ⅰ and Ⅱ disease. Thus, the prognostic role of EpCAM in GC is still unclear and the association between clinical characteristics of GC patients and EpCAM expression levels needs to be further elucidated. These conflicting data were likely due to the small sample size and intratumoral heterogeneity of GC, which was observed in the studies.

This meta-analysis is the first study to systematically estimate EpCAM expression and its relationship with clinicopathological characteristics and OS rates in GC patients. We calculated pooled RRs to study the correlation of EpCAM with patient clinical characteristics. This showed that EpCAM expression was positively related with poor histological type, lymph node metastasis, high-grade of TNM stage and tumor size (> 5 cm), depth of invasion (T3-T4) and tumor location (lower part of the stomach) in GC patients. This suggests that GC patients with the above-mentioned clinical characteristics were more likely to have a poorer prognosis after the diagnosis was made.

The biological function of EpCAM may be implicated in the relationship between EpCAM expression and cancer outcome mentioned above. Recently, studies have reported that overexpression of EpCAM occurs in a variety of cancers, for example colon, breast and ovarian, and most human adenocarcinomas. Furthermore, it has effects on differentiation, proliferation and migration of cancer cells.

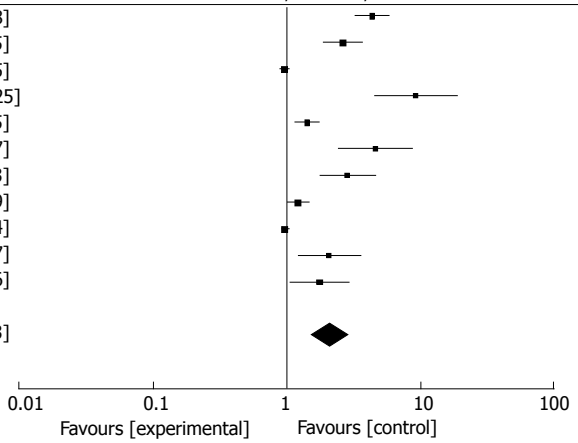
There are certain limitations in the present meta-analysis that need to be pointed out. First, although we tried to avoid biases in performing this meta-analysis, publication bias may have occurred because only published studies were included in the meta-analysis even if the statistical test did not show it. Second, we did not find any significant association between EpCAM expression and OS in GC patients. It is very likely that limited research has been done on EpCAM and its relationship with prognosis. Only three studies were included in the OS meta-analysis, with a relatively small sample size of 831 patients. Finally, there was heterogeneity between studies present in this article, with a P-value < 0.05, especially in the evaluation of the relationship between EpCAM expression and some adverse clinical parameters. This was related to insufficient sample size and a lack of certain original data. To adjust for this, we used a trim-and-fill method in the random-effect model to make the outcomes statistically credible.

In conclusion, this meta-analysis suggests that the expression of EpCAM is associated with poor clinicopathological features of GC. However, because of the heterogeneity of included studies and bias of meta-analysis, our conclusions need to be interpreted with caution. More

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95%CI
Feride Kroepil 2013	126	126	37	166	9.7%	4.44 [3.35, 5.88]
Jia-jia Yang 2014	48	53	24	71	9.4%	2.68 [1.91, 3.75]
Li Li 2012	179	221	257	307	10.3%	0.97 [0.89, 1.05]
Ming-dian Lu 2011	84	95	7	75	7.1%	9.47 [4.66, 19.25]
Shi-bin Yang 2012	56	60	39	60	10.0%	1.44 [1.18, 1.75]
Wang-qing Zhang 2011	34	40	8	44	7.6%	4.67 [2.46, 8.87]
Wang-qing Zhang 2014	30	31	12	36	8.7%	2.90 [1.82, 4.63]
Xiao-tong Sun 2010	52	54	28	36	10.1%	1.24 [1.03, 1.49]
Yuan-Yu Wang 2013	247	289	354	404	10.3%	0.98 [0.92, 1.04]
Yun-xiang Peng 2011	21	27	10	27	8.3%	2.10 [1.23, 3.57]
Zhi-xue Fang 2010	46	79	12	37	8.5%	1.80 [1.09, 2.96]
Total (95%CI)		1075		1263	100.0%	2.16 [1.54, 3.03]
Total events	923		788			

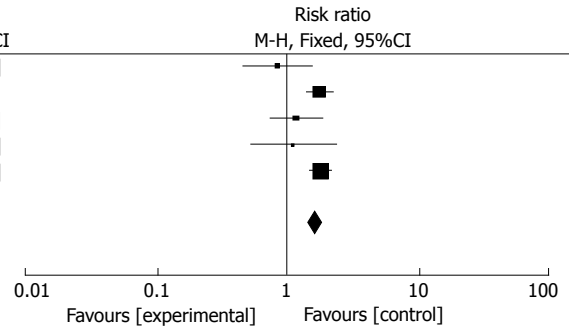
Heterogeneity: Tau^2 = 0.29; χ^2 = 375.56, df = 10 (P < 0.00001); I^2 = 97%
Test for overall effect: Z = 4.45 (P < 0.00001)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95%CI
Jia-jia Yang 2014	17	48	10	24	6.9%	0.85 [0.46, 1.56]
Li Li 2012	100	179	80	257	34.2%	1.79 [1.44, 2.24]
Ming-dian Lu 2011	38	66	12	25	9.1%	1.20 [0.76, 1.90]
Wang-qing Zhang 2014	25	37	3	5	2.8%	1.13 [0.53, 2.38]
Yuan-Yu Wang 2013	141	247	110	354	47.1%	1.84 [1.52, 2.22]
Total (95%CI)		577		665	100.0%	1.68 [1.47, 1.91]
Total events	321		215			

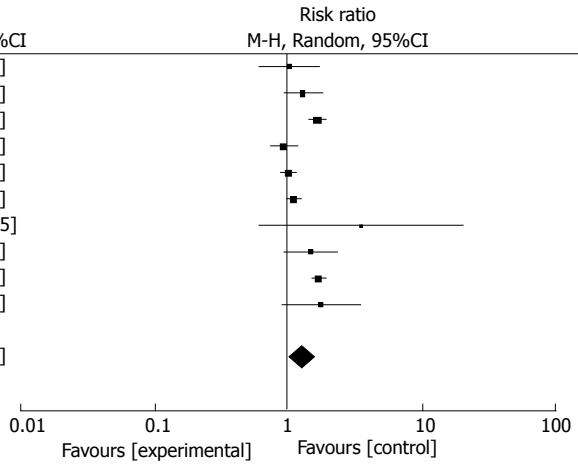
Heterogeneity: χ^2 = 9.18, df = 4 (P = 0.06); I^2 = 56%
Test for overall effect: Z = 7.69 (P < 0.00001)



C

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95%CI
Feride Kroepil 2013	44	126	12	37	7.5%	1.08 [0.64, 1.82]
Jia-jia Yang 2014	41	48	15	24	10.6%	1.37 [0.98, 1.90]
Li Li 2012	149	179	121	257	13.5%	1.77 [1.53, 2.04]
Ming-dian Lu 2011	52	66	20	25	12.2%	0.98 [0.78, 1.24]
P Went 2016	282	305	32	37	13.6%	1.07 [0.94, 1.22]
Shi-bin Yang 2012	55	56	33	39	13.6%	1.16 [1.01, 1.33]
Wang-qing Zhang 2014	28	37	1	5	1.3%	3.78 [0.65, 22.05]
Xiao-tong Sun 2010	41	46	8	14	8.4%	1.56 [0.98, 2.48]
Yuan-Yu Wang 2013	212	247	168	354	13.8%	1.81 [1.60, 2.04]
Zhi-xue Fang 2010	36	46	5	12	5.6%	1.88 [0.95, 3.73]
Total (95%CI)		1156		804	100.0%	1.37 [1.11, 1.68]
Total events	940		415			

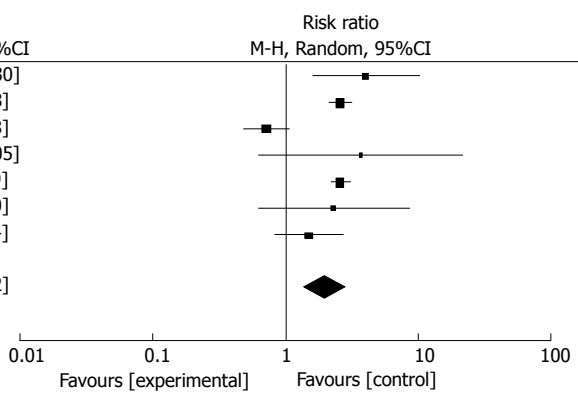
Heterogeneity: Tau^2 = 0.08; χ^2 = 72.75, df = 9 (P < 0.00001); I^2 = 88%
Test for overall effect: Z = 2.96 (P = 0.003)



D

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95%CI
Jia-jia Yang 2014	33	48	4	24	10.5%	4.13 [1.65, 10.30]
Li Li 2012	157	179	85	257	22.0%	2.65 [2.21, 3.18]
Ming-dian Lu 2011	31	66	16	25	18.9%	0.73 [0.50, 1.08]
Wang-qing Zhang 2014	28	37	1	5	4.3%	3.78 [0.65, 22.05]
Yuan-Yu Wang 2013	220	247	119	354	22.3%	2.65 [2.27, 3.09]
Yun-xiang Peng 2011	10	21	2	10	6.6%	2.38 [0.64, 8.90]
Zhi-xue Fang 2010	35	46	6	12	15.4%	1.52 [0.84, 2.74]
Total (95%CI)		644		687	100.0%	2.02 [1.35, 3.02]
Total events	514		233			

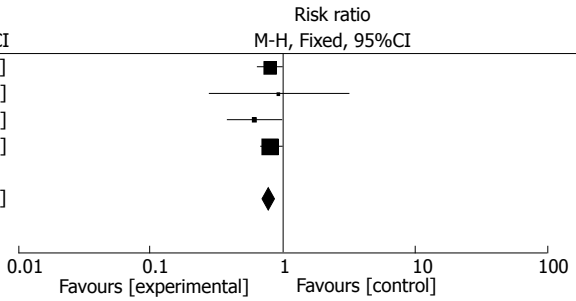
Heterogeneity: Tau^2 = 0.18; χ^2 = 42.27, df = 6 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 3.41 (P = 0.0007)



E

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95%CI
Li Li 2012	79	179	139	257	38.5%	0.82 [0.67, 1.00]
Ming-dian Lu 2011	23	84	2	7	1.2%	0.96 [0.28, 3.25]
Shi-bin Yang 2012	19	56	21	39	8.4%	0.63 [0.40, 1.01]
Yuan-Yu Wang 2013	107	247	187	354	51.9%	0.82 [0.69, 0.98]
Total (95%CI)		566		657	100.0%	0.80 [0.71, 0.91]
Total events	228		349			

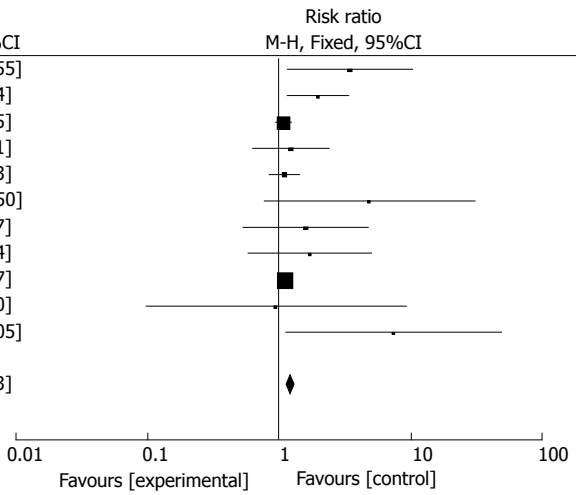
Heterogeneity: $Tau^2 = 1.20$, df = 3 ($P = 0.75$); $I^2 = 0\%$
Test for overall effect: $Z = 3.40$ ($P = 0.0007$)



F

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95%CI
Du Wenqi 2008	30	74	3	26	1.1%	3.51 [1.17, 10.55]
Jia-jia Yang 2014	36	48	9	24	3.1%	2.00 [1.16, 3.44]
Li Li 2012	127	179	166	257	34.8%	1.10 [0.96, 1.25]
Ming-dian Lu 2011	60	84	4	7	1.9%	1.25 [0.65, 2.41]
Shi-bin Yang 2012	43	56	27	39	8.1%	1.11 [0.86, 1.43]
Wang-qing Zhang 2011	21	34	1	8	0.4%	4.94 [0.78, 31.50]
Wang-qing Zhang 2014	24	37	2	5	0.9%	1.62 [0.54, 4.87]
Xiao-tong Sun 2010	17	46	3	14	1.2%	1.72 [0.59, 5.04]
Yuan-Yu Wang 2013	180	247	227	354	47.7%	1.14 [1.02, 1.27]
Yun-xiang Peng 2011	2	21	1	10	0.3%	0.95 [0.10, 9.30]
Zhi-xue Fang 2010	29	46	1	12	0.4%	7.57 [1.14, 50.05]
Total (95%CI)		872		756	100.0%	1.23 [1.13, 1.33]
Total events	569		444			

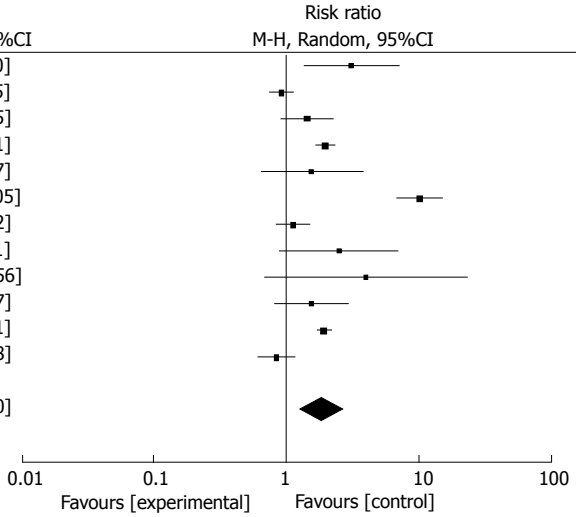
Heterogeneity: $\chi^2 = 18.48$, df = 10 ($P = 0.05$); $I^2 = 46\%$
Test for overall effect: $Z = 4.91$ ($P < 0.00001$)



G

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95%CI
Du Wenqi 2008	45	74	5	26	7.2%	3.16 [1.41, 7.10]
Feride Kroepil 2013	92	125	29	37	10.1%	0.94 [0.77, 1.15]
Jia-jia Yang 2014	35	48	12	24	9.1%	1.46 [0.94, 2.25]
Li Li 2012	157	179	113	257	10.2%	1.99 [1.72, 2.31]
Ming-dian Lu 2011	57	84	3	7	6.8%	1.58 [0.66, 3.77]
P Went 2006	241	357	26	397	9.4%	10.31 [7.06, 15.05]
Shi-bin Yang 2012	41	56	25	39	9.8%	1.14 [0.86, 1.52]
Wang-qing Zhang 2011	19	30	3	12	6.1%	2.53 [0.92, 7.01]
Wang-qing Zhang 2014	30	37	1	5	3.3%	4.05 [0.70, 23.56]
Xiao-tong Sun 2010	31	46	6	14	8.1%	1.57 [0.83, 2.97]
Yuan-Yu Wang 2013	220	247	161	354	10.2%	1.96 [1.73, 2.21]
Zhi-xue Fang 2010	33	46	10	12	9.7%	0.86 [0.63, 1.18]
Total (95%CI)		1329		1184	100.0%	1.89 [1.28, 2.80]
Total events	1001		394			

Heterogeneity: $Tau^2 = 0.38$; $\chi^2 = 213.80$, df = 11 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 3.21$ ($P = 0.001$)



H

Study or subgroup	log [hazard ratio]	SE	Weight	Hazard ratio IV, Random, 95%CI
I Songun 2005	-1.03	0.24	33.5%	0.36 [0.22, 0.57]
Li Li 2012	1.61	0.26	33.3%	5.00 [3.01, 8.33]
Shi-bin Yang 2012	0.42	0.27	33.2%	1.52 [0.90, 2.58]
Total (95%CI)			100.0%	1.39 [0.30, 6.48]

Heterogeneity: $Tau^2 = 1.78$; $\chi^2 = 56.20$, df = 2 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 0.42$ ($P = 0.67$)

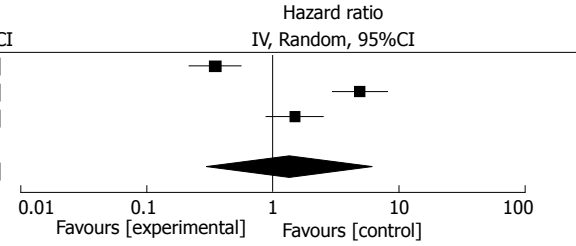


Figure 2 Meta-analysis Forest plot. A: Meta-analysis Forest plot concerning the expression level of epithelial cellular adhesion molecule with gastric cancer between samples of gastric cancer and normal ones; B: Meta-analysis Forest plot concerning tumor size; C: Meta-analysis Forest plot concerning depth of invasion; D: Meta-analysis Forest plot concerning TNM stage; E: Meta-analysis Forest plot concerning tumor location; F: Meta-analysis Forest plot concerning histologic differentiation; G: Meta-analysis Forest plot concerning lymph node metastasis; H: Meta-analysis Forest plot concerning overall survival rate.

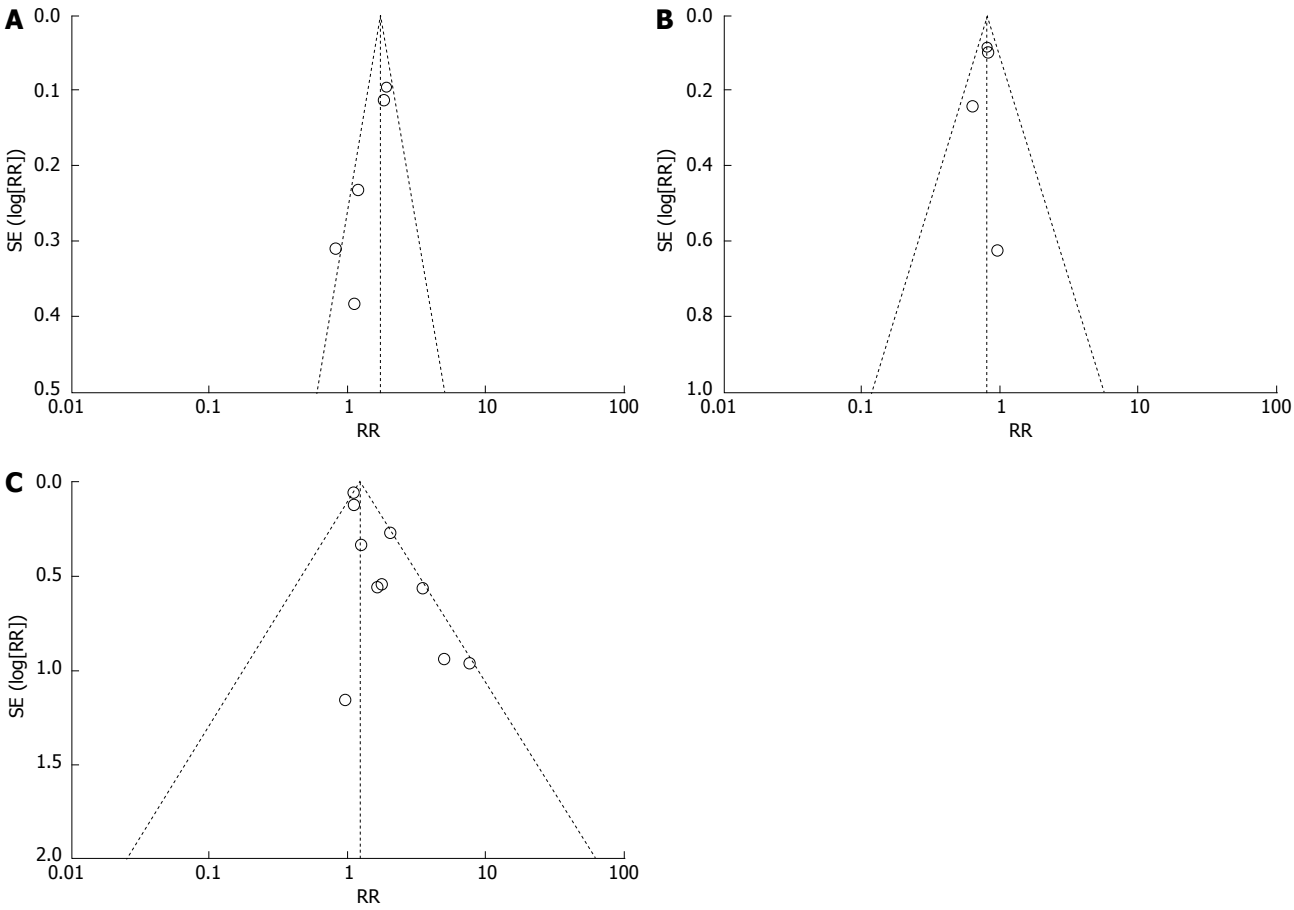


Figure 3 Funnel plot of tumor size (A), tumor location (B) and histologic differentiation (C). RR: Risk ratio.

clinical studies will be required to determine the association between the expression of EpCAM and GC prognosis.

COMMENTS

Background

Although gastric cancer (GC) rates have decreased substantially in the past few decades, it remains the second most common cause of cancer-related death worldwide. Although several studies showed high expression of epithelial cellular adhesion molecule (EpCAM) in GC, which was related to cancer progression and survival prognosis, there is no comprehensive study on the correlation of EpCAM expression with survival prognosis or the effects of EpCAM expression on clinicopathologic characteristics in GC patients.

Research frontiers

This meta-analysis was conducted to determine the association between high expression of EpCAM and clinicopathological features and progression as well as prognosis of GC.

Innovations and breakthroughs

Studies that had examined the association between high expression of EpCAM and GC risk were identified by searching electronic databases PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature database.

Applications

This meta-analysis indicates that EpCAM contributes to GC risk, which acts as a prognostic factor and a marker of poor outcome.

Peer-review

The authors reported the "Expression of epithelial cellular adhesion molecule in gastric cancer: A meta-analysis". These findings are important to those with closely related research interests. It is well organized and systemically analysed.

REFERENCES

1 **Chan AO**, Wong BC, Lam SK. Gastric cancer: past, present and future. *Can J Gastroenterol* 2001; **15**: 469-474 [PMID: 11493951]
2 **Kroepil F**, Dulian A, Vallböhmer D, Geddert H, Krieg A, Vay C, Topp SA, am Esch JS, Baldus SE, Gires O, Knoefel WT, Stoecklein NH. High EpCAM expression is linked to proliferation and lauren classification in gastric cancer. *BMC Res Notes* 2013; **6**: 253 [PMID: 23830302 DOI: 10.1186/1756-0500-6-253]
3 **Spizzo G**, Fong D, Wurm M, Ensinger C, Obrist P, Hofer C, Mazzoleni G, Gastl G, Went P. EpCAM expression in primary tumour tissues and metastases: an immunohistochemical analysis. *J Clin Pathol* 2011; **64**: 415-420 [PMID: 21415054 DOI: 10.1136/jcp.2011.090274]
4 **Martowicz A**, Spizzo G, Gastl G, Untergasser G. Phenotype-dependent effects of EpCAM expression on growth and invasion of human breast cancer cell lines. *BMC Cancer* 2012; **12**: 501 [PMID: 23110550 DOI: 10.1186/1471-2407-12-501]
5 **Went P**, Vasei M, Bubendorf L, Terracciano L, Tornillo L, Riede U, Kononen J, Simon R, Sauter G, Baeuerle PA. Frequent high-level expression of the immunotherapeutic target Ep-CAM in colon, stomach, prostate and lung cancers. *Br J Cancer* 2006; **94**: 128-135 [PMID: 16404366]
6 **Imano M**, Itoh T, Satou T, Yasuda A, Nishiki K, Kato H, Shiraishi O, Peng YF, Shinkai M, Tsubaki M, Yasuda T, Imamoto H, Nishida S, Takeyama Y, Furkawa H, Okuno K, Shiozaki H. High expression of epithelial cellular adhesion molecule in peritoneal metastasis of gastric cancer. *Target Oncol* 2013; **8**: 231-235 [PMID: 23161021

DOI: 10.1007/s11523-012-0239-4]
7 **Horikawa M**, Iinuma H, Inoue T, Ogawa E, Fukushima R. Clinical significance of intraperitoneal CD44 mRNA levels of magnetically separated CD45-negative EpCAM-positive cells for peritoneal recurrence and prognosis in stage II and III gastric cancer patients. *Oncol Rep* 2011; **25**: 1413-1420 [PMID: 21331451 DOI: 10.3892/or.2011.1191]
8 **Du W**, Ji H, Cao S, Wang L, Bai F, Liu J, Fan D. EpCAM: a potential antimetastatic target for gastric cancer. *Dig Dis Sci* 2010; **55**: 2165-2171 [PMID: 19941073 DOI: 10.1007/s10620-009-1033-8]
9 **Warneke VS**, Behrens HM, Haag J, Krüger S, Simon E, Mathiak M, Ebert MP, Röcken C. Members of the EpCAM signalling pathway are expressed in gastric cancer tissue and are correlated with patient prognosis. *Br J Cancer* 2013; **109**: 2217-2227 [PMID: 24008668 DOI: 10.1038/bjc.2013.536]
10 **Heideman DA**, Snijders PJ, Craanen ME, Bloemena E, Meijer CJ, Meuwissen SG, van Beusechem VW, Pinedo HM, Curiel DT, Haisma HJ, Gerritsen WR. Selective gene delivery toward gastric and esophageal adenocarcinoma cells via EpCAM-targeted adenoviral vectors. *Cancer Gene Ther* 2001; **8**: 342-351 [PMID: 11477454]
11 **Fong D**, Seeber A, Terracciano L, Kasal A, Mazzoleni G, Lehne F, Gastl G, Spizzo G. Expression of EpCAM(MF) and EpCAM(MT) variants in human carcinomas. *J Clin Pathol* 2014; **67**: 408-414 [PMID: 24465008 DOI: 10.1136/jclinpath-2013-201932]
12 **van der Gun BT**, Melchers LJ, Ruiters MH, de Leij LF, McLaughlin PM, Rots MG. EpCAM in carcinogenesis: the good, the bad or the ugly. *Carcinogenesis* 2010; **31**: 1913-1921 [PMID: 20837599 DOI: 10.1093/carcin/bgq187]
13 **Imano M**, Okuno K. Treatment strategies for gastric cancer patients with peritoneal metastasis. *Surg Today* 2014; **44**: 399-404 [PMID: 23677598 DOI: 10.1007/s00595-013-0603-8]
14 **Okada T,** Nakamura T, Watanabe T, Onoda N, Ashida A, Okuyama R, Ito K. Coexpression of EpCAM, CD44 variant isoforms and claudin-7 in anaplastic thyroid carcinoma. *PLoS One* 2014; **9**: e94487 [DOI: 10.1371/journal.pone.0094487]
15 **Ralhan R**, Cao J, Lim T, Macmillan C, Freeman JL, Walfish PG. EpCAM nuclear localization identifies aggressive thyroid cancer and is a marker for poor prognosis. *BMC Cancer* 2010; **10**: 331 [PMID: 20579375 DOI: 10.1186/1471-2407-10-331]
16 **Wang YY**, Li L, Zhao ZS, Wang YX, Ye ZY, Tao HQ. L1 and epithelial cell adhesion molecules associated with gastric cancer progression and prognosis in examination of specimens from 601 patients. *J Exp Clin Cancer Res* 2013; **32**: 66 [PMID: 24422715 DOI: 10.1186/1756-9966-32-66]
17 **Balzar M**, Winter MJ, de Boer CJ, Litvinov SV. The biology of the 17-1A antigen (Ep-CAM). *J Mol Med* (Berl) 1999; **77**: 699-712 [PMID: 10606205]
18 **Varga M**, Obrist P, Schneeberger S, Mühlmann G, Felgel-Farnholz C, Fong D, Zitt M, Brunhuber T, Schäfer G, Gastl G, Spizzo G. Overexpression of epithelial cell adhesion molecule antigen in gallbladder carcinoma is an independent marker for poor survival. *Clin Cancer Res* 2004; **10**: 3131-3136 [PMID: 15131054]
19 **Soysal SD**, Muenst S, Barbie T, Fleming T, Gao F, Spizzo G, Oertli D, Viehl CT, Obermann EC, Gillanders WE. EpCAM expression varies significantly and is differentially associated with prognosis in the luminal B HER2(+), basal-like, and HER2 intrinsic subtypes of breast cancer. *Br J Cancer* 2013; **108**: 1480-1487 [PMID: 23519058 DOI: 10.1038/bjc.2013.80]
20 **Chaudry MA**, Sales K, Ruf P, Lindhofer H, Winslet MC. EpCAM an immunotherapeutic target for gastrointestinal malignancy: current experience and future challenges. *Br J Cancer* 2007; **96**: 1013-1019 [PMID: 17325709]
21 **Went PT**, Lugli A, Meier S, Bundi M, Mirlacher M, Sauter G, Dirnhofer S. Frequent EpCam protein expression in human carcinomas. *Hum Pathol* 2004; **35**: 122-128 [PMID: 14745734]
22 **Wenqi D**, Li W, Shanshan C, Bei C, Yafei Z, Feihu B, Jie L, Daiming F. EpCAM is overexpressed in gastric cancer and its downregulation suppresses proliferation of gastric cancer. *J Cancer Res Clin Oncol* 2009; **135**: 1277-1285 [PMID: 19294417 DOI: 10.1007/s00432-009-0569-5]
23 **Songun I**, Litvinov SV, van de Velde CJ, Pals ST, Hermans J, van Krieken JH. Loss of Ep-CAM (CO17-1A) expression predicts survival in patients with gastric cancer. *Br J Cancer* 2005; **92**: 1767-1772 [PMID: 15870832]

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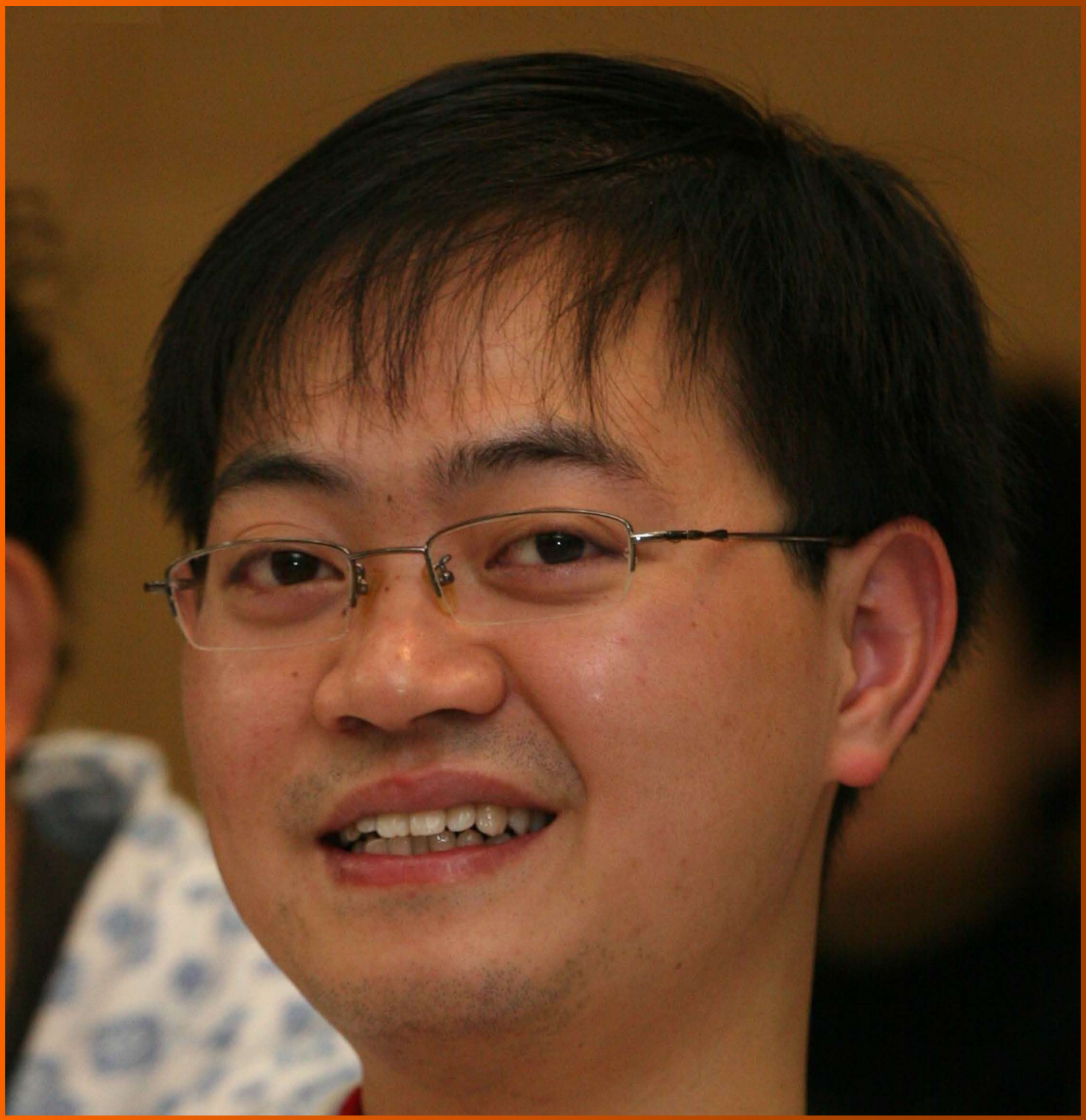

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Environmental tobacco smoke exposure and lung cancer: A systematic review

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Author contributions: Lee PN, Fry JS and Forey BA planned the study; Hamling JS and Thornton AJ carried out the literature searches, assisted by Lee PN and Forey BA; Fry JS, Forey BA, Hamling JS and Thornton AJ carried out the data entry which was independently checked by one of these or Lee PN; Lee PN and Forey BA discussed any difficulties in interpreting published data or in the appropriate methods for derivation of RRs; Forey BA and Hamling JS conducted the main statistical analyses, and Fry JS the bias analyses along lines discussed and agreed with Lee PN; Lee PN drafted the paper, with the assistance of Thornton AJ, which was critically reviewed by the other authors.

Conflict-of-interest statement: Lee PN, Director of P.N. Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies including the sponsors of this study. Fry JS, Forey BA and Hamling JS are employees of, and Thornton AJ a consultant to, P.N. Lee Statistics and Computing Ltd.

Data sharing statement: Supplementary Files provide: (1) further information on the methods; (2) fuller description and results of the confounder/misclassification analyses; (3) description of reasons for rejection of some papers; and (4) fuller results of the main meta-analyses. Copies of the database files are available on request from the corresponding author at peterlee@pnlee.co.uk.

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Abstract

AIM: To review evidence relating passive smoking to lung cancer risk in never smokers, considering various major sources of bias.

METHODS: Epidemiological prospective or case-control studies were identified which provide estimates of relative risk (RR) and 95%CI for never smokers for one or more of seven different indices of exposure to environmental tobacco smoke (ETS): The spouse; household; workplace; childhood; travel; social and other; and total. A wide range of study details were entered into a database, and the RRs for each study, including descriptions of the comparisons made, were entered into a linked database. RRs were derived where necessary. Results were entered, where available, for all lung cancer, and for squamous cell cancer and adenocarcinoma. "Most adjusted" results were entered based on results available, adjusted for the greatest number of potential confounding variables. "Least adjusted" results were also entered, with a preference for results adjusted at least for age for prospective studies. A pre-planned series of fixed-effects and random-effects meta-analyses were conducted. Overall analyses and analyses by continent were run for each exposure index, with results for spousal smoking given by sex, and results for childhood exposure given by source of ETS exposure. For spousal exposure, more extensive analyses provide

results by various aspects of study design and definition of the RR. For smoking by the husband (or nearest equivalent), additional analyses were carried out both for overall risk, and for risk per 10 cigarettes per day smoked by the husband. These adjusted for uncontrolled confounding by four factors (fruit, vegetable and dietary fat consumption, and education), and corrected for misclassification of smoking status of the wife. For the confounding adjustment, estimates for never smoking women were derived from publications on the relationship of the four factors to both lung cancer risk and at home ETS exposure, and on the correlations between the factors. The bias due to misclassification was calculated on the basis that the proportion of ever smokers denying smoking is 10% in Asian studies and 2.5% elsewhere, and that those who deny smoking have the same risk as those who admit it. This approach, justified in previous work, balances higher true denial rates and lower risk in deniers compared to non-deniers.

RESULTS: One hundred and two studies were identified for inclusion, published in 1981 onwards, 45 in Asia, 31 in North America, 21 in Europe, and five elsewhere. Eighty-five were of case-control design and 17 were prospective. Significant ($P < 0.05$) associations were noted, with random-effects of (RR = 1.22, 95%CI: 1.14-1.31, n = 93) for smoking by the husband (RR = 1.14, 95%CI: 1.01-1.29, n = 45) for smoking by the wife (RR = 1.22, 95%CI: 1.15-1.30, n = 47) for workplace exposure (RR = 1.15, 95%CI: 1.02-1.29, n = 41) for childhood exposure, and (RR = 1.31, 95%CI: 1.19-1.45, n = 48) for total exposure. No significant association was seen for ETS exposure in travel (RR = 1.34, 95%CI: 0.94-1.93, n = 8) or in social situations (RR = 1.01, 95%CI: 0.82-1.24, n = 15). A significant negative association (RR = 0.78, 95%CI: 0.64-0.94, n = 8) was seen for ETS exposure in childhood, specifically from the parents. Significant associations were also seen for spousal smoking for both squamous cell carcinoma (RR = 1.44, 95%CI: 1.15-1.80, n = 24) and adenocarcinoma (RR = 1.33, 95%CI: 1.17-1.51, n = 30). Results generally showed marked heterogeneity between studies. For smoking by either the husband or wife, where 119 RR estimates gave an overall estimate of (RR = 1.21, 95%CI: 1.14-1.29), the heterogeneity was highly significant ($P < 0.001$), with evidence that the largest RRs were seen in studies published in 1981-89, in small studies (1-49 cases), and for estimates unadjusted by age. For smoking by the husband, the additional analyses showed that adjustment for the four factors reduced the overall (RR = 1.22, 95%CI: 1.14-1.31) based on 93 estimates to (RR = 1.14, 95%CI: 1.06-1.22), implying bias due to uncontrolled confounding of 7%. Further correction for misclassification reduced the estimate to a marginally non-significant (RR = 1.08, 95%CI: 0.999-1.16). In the fully adjusted and corrected analyses, there was evidence of an increase in Asia (RR = 1.18, 95%CI: 1.07-1.30, n = 44), but not in other regions (RR = 0.96, 95%CI: 0.86-1.07, n = 49). Studies published in the 1980's, studies providing dose-response data, and studies only providing results unadjusted for age showed elevated RRs, but later published studies, studies not providing dose-response data, and studies adjusting for age did not. The pattern of results for RRs per 10 cigs/d was similar, with no significant association in the adjusted and corrected results (RR = 1.03, 95%CI: 0.994-1.07).

CONCLUSION: Most, if not all, of the ETS/lung cancer association can be explained by confounding adjustment and misclassification correction. Any causal relationship is not convincingly demonstrated.

Key words: Passive smoking; Lung neoplasms; Dose-response; Meta-analysis; Review; Confounding factors (epidemiology); Misclassification

Core tip: We present an up-to-date meta-analysis of the evidence relating non-smoker lung cancer to environmental tobacco smoke (ETS) exposure. We demonstrate a clear risk increase for spousal, at-home, workplace and total exposure, but not childhood exposure. For husband smoking, the relative risk (RR) is estimated as (RR = 1.22, 95%CI: 1.14-1.31). However, adjustment for confounding by education and dietary variables, and correction for misclassified wife's smoking reduces it to (RR = 1.08, 95%CI: 0.999-1.16). Given the other data limitations and biases we discuss, one cannot reliably conclude that any true ETS effect on lung cancer risk exists. Our results suggest caution in drawing inferences from weak epidemiological associations where known biases exist.

Lee PN, Fry JS, Forey BA, Hamling JS, Thornton AJ. Environmental tobacco smoke exposure and lung cancer: A systematic review. *World J Meta-Anal* 2016; 4(2): 10-43 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i2/10.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i2.10

INTRODUCTION

It has been widely accepted that environmental tobacco smoke (ETS) exposure increases lung cancer risk, based on various authoritative reviews[1]. However, it was suggested some years ago[2] that a substantial part, if not all, of the relationship may be due to bias resulting from confounding by other lung cancer risk factors, and misclassification of smoking habits, with some self-reported never smokers actually being smokers. While there have been various meta-analyses of the evidence in the last 20 years[3-10]. these are often limited to specific indices of exposure or regions, and typically do not include formal adjustments for potential biases. They also do not take into account all the more recent studies, with over 100 studies published by now, many relatively recent.

The objective of this review, therefore, is to present an up-to-date comprehensive meta-analysis of the

available evidence which relates ETS exposure to lung cancer risk among never smokers, considering exposure from various sources, and illustrating the potential magnitude of the bias that can arise from confounding and misclassification of smoking.

MATERIALS AND METHODS

Introduction

The analyses presented were conducted in three stages. First, results of meta-analysis are presented relating a range of indices of ETS exposure to risk of lung cancer. Second, for two indices (spousal smoking and amount smoked by the spouse), individual study estimates for females are adjusted for the effects of confounding for selected variables (fruit consumption, vegetable consumption, dietary fat consumption and education) and revised meta-analyses conducted. Third, further adjustments are made for the biasing effects of misclassification of smoking status. The materials and methods section is therefore divided accordingly.

Study inclusion and exclusion criteria

Attention was restricted to epidemiological prospective or case-control studies published up to and including July 2015, which involved five or more lung cancers, and which provided relative risk (RR) estimates for never (or virtually never) smokers for one or more defined ETS exposure types or dose-related ETS indices. The "exposure types" compare subjects exposed and unexposed to ETS from seven different sources: Spouse; household; workplace; childhood; travel; social and other; and total, the final category including biochemical assessments of exposure. The "dose-related indices" concern ETS exposure in terms of amount smoked, duration of smoking and the number of smokers the subject was exposed to. ETS exposure from pipe/cigar only was ignored. Note that the term "relative risk" is taken to include estimates of it, such as the odds ratio or hazard ratio.

Studies using near equivalent definitions of "never smokers" were accepted when stricter definitions were unavailable, so never smokers could include occasional smokers, those with a minimal lifetime duration of smoking or number smoked, or ex-smokers who had quit at least 20 years previously.

Literature searches

Up until July 2015 potentially relevant papers were regularly sought from MEDLINE searches (using search terms "tobacco smoke pollution" and "lung neoplasm"), from files on smoking and health which were collected for many years within our company, and from references which were cited in the papers obtained. At the end of the process no paper examined cited a possibly relevant paper which had not been previously examined.

Study identification

Relevant papers were separated into studies, noting where there were multiple papers per study or multiple studies per paper, and any overlaps between studies. Each study was uniquely referenced by a $\leqslant$ 6 character code, based on the name of the principal author, with a suffix indicating where the same author had reported on multiple studies.

Data recorded

Data were entered on a study database, and also on a linked RR database. The structure and content of the databases are described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 1.pdf.

In brief, a study database record describes the study design, the available data and a previously described index of study quality[11]. Typically there are multiple records per study on the RR database, each record holding a detailed description of a specific comparison made and the corresponding RR and its 95%CI.

RR derivation

When available, adjusted RRs and CIs were entered. Unadjusted estimates were derived from the 2 × 2 table, using standard methodology[12], any differences between calculated and author-provided estimates being noted. Other methodologies were used where required to derive estimates, those more commonly used[13,14] being described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 1.pdf.

Identifying the RRs to enter

RRs were entered, if available, relating to various pre-defined combinations of type of lung cancer, index of smoking, confounders considered, and strata. The combinations are described in the following sections.

Type of lung cancer: Results were entered for overall lung cancer, squamous cell carcinoma and adenocarcinoma, or their nearest equivalents for which data were available.

Smoking indices: The intention was to enter RRs comparing subjects exposed and unexposed to the various indices of ETS defined above. Though RRs for exposure to smoking by the spouse should ideally be derived from data only for married subjects, we also allowed RRs from studies where unmarried subjects were included in the reference group. Similarly, RRs for workplace exposure could include non-working subjects. For the "household" and "childhood" categories, RRs were entered for all possible sources recorded by the studies, but for the "travel" and "social" categories, if more than one index of exposure was available, only that representing the greatest number of exposed subjects was entered. RRs were entered for all available timings of adult exposure, but for childhood, only RRs for the earliest exposure were entered. "Total" exposure was defined as exposure to two or more types of exposure, or biochemical assessment of overall exposure. For dose-related exposure indices, RRs were entered for each level of exposure relative to a common base level. RRs were entered, where available, using denominators

representing both "no exposure to the specific type of ETS" and "no exposure to any ETS".

Confounders: For case-control studies, we entered results adjusted for the most potential confounders available, and also adjusted for fewest. For prospective studies, we entered results adjusted for age and the most confounders, and for age and the fewest, and unadjusted results were entered only where there were no age-adjusted results. We describe these alternative RRs as "most-adjusted" and "least-adjusted".

Strata: We only entered results stratified by sex or age. Combined sex results were only entered if results by sex were unavailable. We entered results for all ages and for separate age groups. Specifically for spousal exposure (or nearest equivalent - see "analyses conducted" below), where an adjusted RR was available only for combined sexes but numbers of cases and controls were given by sex, split-sex estimates were entered, assuming that the RR applied to each sex, with separate CIs estimated for males and females.

Meta-analyses

Analyses conducted: The series of meta-analyses conducted was pre-planned. For a given exposure type, a set of up to 20 analyses was conducted. Meta-analyses 1 and 2 used the overall data available, while meta-analyses 3 and 4 were separated by region (North America, Europe, Asia or other regions), with meta-analyses 1 and 3 using most-adjusted and 2 and 4 least-adjusted data. Analyses 5-20 were based on most-adjusted data only and studied variation by other factors, as described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 1.pdf.

The primary index of exposure used was "spousal smoking (or nearest equivalent)" where, for studies which provided no results for spousal exposure, results for household, total or both spousal/home and other exposure were chosen instead. This identified a single exposure definition for each study. For overall lung cancer, the full set of 20 meta-analyses was carried out restricted to females, and unrestricted on sex. Further meta-analyses for the principal index of exposure corresponded to meta-analyses 1 to 4 only. These included analyses for spousal smoking (or nearest equivalent) for males, spousal smoking (specifically) for females, males and unrestricted on sex, and analyses for spousal smoking (or nearest equivalent) for squamous cell carcinoma and for adenocarcinoma, each for females, males and unrestricted on sex.

Analyses for the other types of exposure were run only for overall lung cancer, without restriction on sex, and were equivalent to meta-analyses 1-4 only. The childhood and household exposure analyses were run using alternative indices, depending on the available data, as described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 1.pdf.

Selecting RRs for the meta-analyses: In selecting RRs to include we tried to include all relevant data once only. Where a study had multiple RRs, that used is chosen by an order of preference specific to the meta-analysis. Order of preference may be needed for exposure status and timing, and for the unexposed base. As RR definitions may be sex-specific, the RRs selected may differ by sex. Results for sexes combined are only considered in the absence of sex-specific results.

Conducting the meta-analyses for exposure indices: We conducted fixed-effect and random-effects meta-analysis of study-specific data for the various exposure indices studied as described elsewhere[13]. Heterogeneity was measured by H, the ratio of heterogeneity χ^2 to degrees of freedom. H relates to I^2 statistic[15] by $I^2 = 100 (H - 1)/H$. For all meta-analyses, results of publication bias tests using the Egger method[16] were also given.

Results are displayed in forest plots. Within each plot, studies are identified by their reference code, and listed in order of RR. Most of the plots are also grouped by region. The study estimates are shown both as numbers and in graphical form logarithmically. In the latter representation an RR is shown as a square, the area of which is proportional to its weight, its inverse-variance. Arrows warn if the CI goes outside the range of the plot. Random-effects estimates are also presented, overall or by region, shown by a diamond whose width indicates the 95%CI.

Carrying out meta-analyses for number of cigarettes smoked by the husband: The methods used are as described elsewhere[17], and are summarized here. The underlying model assumes that, when comparing two groups differing in exposure by dose d, log RR is estimated by βd. For each study, given data at each level of exposure consisting of the dose level, the number of cases, and the number of controls (or subjects at risk), β and its standard error (SEβ) are estimated by the method of Greenland and Longnecker[18], This can be applied to studies with only two levels (unexposed and exposed), and also to confounder-corrected RRs and 95%CIs, by estimating pseudo-counts using the method of Hamling[14]. Estimates of β and SEβ from each study are then meta-analysed as described above. The method of estimating midpoint doses for intervals such as 1-19 or 20+ cigarettes per day is as described previously[17].

The series of meta-analyses conducted for the estimates of β was similar to that for the exposure indices as described above.

Adjustment for bias due to confounding

The potential confounding variables considered (consumption of fruit, consumption of vegetables, consumption of dietary fat, and education) and the methods used to adjust for them are as described in a previous publication[19] and in

an unpublished updated analysis conducted in 2006[20]. The methods are summarized briefly below.

Estimating the relationship between the four potential confounding variables considered and the risk of lung cancer in never smoking females: The database of studies relating lung cancer risk in never smokers to the four potential confounding variables used in 2001[19] and updated in 2006[20] was used, restricting attention to never smoking females. Exp(β), the increase in risk per dose unit (SDs for dietary variables, years for education), was estimated using methodology equivalent to that described in the previous section. Methods for assigning midpoint dose values for grouped dietary data (*e.g.,* by quintiles), and for education groups were as before[19].

Estimating the differences in fruit, vegetable and fat consumption and in education associated with ETS exposure: The database of studies comparing the distribution of the four potential confounding variables set up in 2001[19] and updated in 2006[20] was used, with attention restricted to never smoking females. For each potential confounding variable, we estimated the difference, δ, in relation to marriage to, or living with, a smoker, in units of SDs for the dietary variables and years for education, using the methodology described earlier[19]. These study-specific estimates of δ were then combined using random-effects meta-analysis.

The basic method for confounder adjustment: As described earlier[19] we assume that the logarithm of L, the lung cancer risk, is linearly related to *n* explanatory factors x_i by:

$$\log L = \beta_o^* + \sum_i^n \beta_i^* x_i \quad (1)$$

Exp(β_o^*) is the background risk that is expected for zero exposure to each factor. Exp (β_i^*) is the multiplicative risk increase expected per unit increase in exposure to the i^{th} factor.

Should data relating lung cancer to the factors be available only univariately the relationship with each factor would be formulated as:

$$\log L = \beta_o + \beta_i x_i \quad (2)$$

where exp(β_i) is the RR for a unit dose increase associated with factor i that is not adjusted for the other risk factors.

The β_i and the β_i^* are related by the matrix equation:

$$B^* = S^{-1}C^{-1}SB \quad (3)$$

Here B* and B are the n × 1 vectors of and β_i, S the n x n standard deviation (SD) matrix, s_i, and C the n x n correlation matrix c_{ij}.

Given B, C and S, we can estimate B*. In our context, there are five factors. i = 1 represents ETS with I = 2…5 the three dietary variables and education. Thus exp(β_i) is the unadjusted risk increase for each unit of increase in ETS exposure, and exp(β_i^*) the adjusted risk increase. The joint confounding effect of the four variables is estimated as exp(β_i)/exp(β_i^*).

Relationship of the factors to lung cancer risk: Estimates of β_i are generally those described in the sub-section "carrying out meta-analyses for number smoked by the husband". However, the basic method assumes that β_i is unadjusted for any of the four potential confounding variables. Where β_i is adjusted for one or more of the variables, we first back-corrected it in order to take out the effect of the adjustment as described earlier[19]. This back-correction procedure avoids double-adjustment for the same factor. Back-correction was also carried out in the following cases: For fruit consumption, where the RR estimate had already been adjusted for vitamin C; for dietary fat, where the RR estimate had already been adjusted for energy intake, for meat, or for cholesterol; and for education, where the RR estimate had already been adjusted for income, for socioeconomic status, or for ownership of a colour TV.

Standard deviations: We estimated s_1, the SD for ETS, directly for each study from the population data by level of exposure as described elsewhere[17]. s_2, s_3 and s_4, the SDs for the dietary variables are 1, since they are measured in units of SD. We took the SD for education as 2.435 years[20].

Correlations: If i = j, c_{ij} = 1. To quantify other correlations, we used the formula:

$$C_{ij} = \delta_j s_1/d_1(\text{average})s_j \quad (4)$$

Here δ_j is a common estimate of the difference in exposure to variable j for living with a smoker (see the sub-section "estimating the differences in fruit…"). s_1 and s_j are as described above, and d_1(average) is the mean ETS exposure for exposed never smokers. Where studies have more than one exposure level, we estimated d_1(average) by weighting on the number of exposed subjects.

To quantify the correlations between the potential confounding variables we used averaged data from seven databases, the five used in 2001[19] and two additional US databases (NHIS2000, NHANES III), as described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf.

Adjustment for bias due to misclassification of smoking status

How the bias arises and what it depends on: Estimates of the RR of lung cancer in self-reported never smoking women associated with marriage to a smoker may be biased if a proportion of the women are actually current or ex-smokers. This bias arises because smokers marry smokers more often than is expected by chance. Misclassified smokers are therefore commoner among those married to a smoker. As shown by Lee and Forey[21], the bias depends mainly on the rate of misclassification, the active smoking risk, the degree to which smoking by spouses is concordant, and the proportions of smokers among subjects and their spouses.

Correction method used: We use the Lee and Forey[21] method for bias correction, assuming joint effects of active smoking and ETS exposure are additive, and the published extension of the method[22].

Concordance ratio: The concordance ratio is defined as the odds of the husband smoking if the wife ever smoked divided by the odds if the wife never smoked. From an earlier review[23] we used an estimate of 3.0.

Study-specific data on active smoking RRs: For each study, estimates were made of the active smoking RR, derived if possible from the source paper itself or another paper using the same study population. Otherwise they were derived from studies in that country, from estimates presented by the EPA[24] or by other methods, as described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf.

Misclassification rates: Misclassified smokers have a lower lung cancer risk than non-misclassified smokers. To take this into account, we followed precedent[21,22] in carrying out the misclassification correction on the basis that those who deny smoking have the same risk as those who admit it, but using lower misclassification rates (10% for Asia, and 2.5% elsewhere) than are observed. Support for the use of these rates is provided elsewhere[21-23,25,26].

Application of the method: RRs for spousal smoking and for amount smoked by the spouse, were calculated: (1) with no adjustment for confounding or correction for misclassification; (2) with adjustment for confounding and no correction for misclassification; and (3) with adjustment for confounding and correction for misclassification.

RESULTS

Studies identified

There were 102 studies which met the inclusion criteria. Some studies were noted to have overlaps with other studies. However, as all overlaps were minor and could not be disentangled, it was decided to ignore them. Tables 1 and 2 give study details including reference(s), location, design, dates, numbers of cases in never smokers, definition of never smoking, ETS exposure measures considered, adjustment variables used, extent of histological confirmation of cases, whether results are available by histological type, and availability of dose-response data. www.pnlee.co.uk/downloads/etslc/23482-supplementary file 3.pdf describes why other publications which could be thought possibly relevant are not considered in our analyses.

Of the 102 studies, 31 were conducted in North America (including 26 in United States), 45 in Asia (including 23 in China, 10 in Japan and 6 in Hong Kong), 21 in Europe (4 in Sweden being the most for any country), and 5 in other locations (including two international studies).

Eighty-five studies were of case-control design and 17 were prospective. Twenty-six studies were published in 1981-1989, 28 in 1990-1999, 32 in 2000-2009 and 16 in or after 2010.

In general, the total number of cases per study was small, with 20 studies based on less than 50 cases, and 29 considering 50-99. Twenty-four studies examined 100-199 cases, 18 200-399 cases, with only 11 based on 400 or more cases.

The most commonly studied index was smoking by the spouse, considered by 55 studies. Smoking by a cohabitant was considered by 47 studies, workplace smoking by 40, and childhood exposure by 41. Travel and social exposures were considered by 5 and 11 studies respectively, and total exposure by 51.

Effect estimates

In what follows, meta-analysis RRs referred to in the text, tables and figures are based on "most-adjusted" estimates, meta-analysis RRs based on "least-adjusted" estimates usually being very similar. The results highlighted are drawn from more detailed analyses for all the exposure indices made available in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 4.pdf, which also shows the "preferences" used in each analysis. This includes some analyses based on "least-adjusted" estimates, and also gives estimates for each individual study included in an analysis. Significance is taken to be at $P < 0.05$ unless otherwise stated. RRs and 95%CIs are normally shown to 2 decimal places. Exceptionally, they are shown to 3 decimal places for the analyses investigating bias due to confounding and misclassification, to show the effects of adjustment and correction more clearly.

Smoking by the spouse

Ninety-three studies provided results relating lung cancer in women to husband's smoking (or nearest equivalent), with 19[27-45] giving significantly raised RRs and 51 non-significantly raised RRs. In contrast 18 studies showed a negative relationship, significant in three studies[46-48]. Five studies gave a RR of 1.00. Two studies could not be included in the meta-analysis, one study[49] reporting no significant effect of passive smoking but giving no further details, with another[50] only giving an odds ratio of 2.2 (1.4-3.7) for greater than 40 smoker-years exposure to passive smoking. There was marked heterogeneity ($P < 0.001$) between the individual study estimates. However, fixed-effect (1.19, 95%CI: 1.14-1.24) and random-effects estimates (1.22, 1.14-1.31) were similar. Based on the Egger test there was no clear evidence of publication bias ($0.05 < P < 0.1$). Further analyses of these data are given in the section "smoking by the husband - detailed analyses" below.

Forty-five studies considered smoking by the wife (or nearest equivalent). Twenty-eight RRs were raised, three[28,39,51] significantly. Fifteen studies reported a negative association, significant in one study[47]. One

Table 1 Selected details of the 102 studies in publication date order

Study ref	Main ref	Other ref	Location	Study design[1]	Study dates[2]			Total cases	Never smoker criteria[3]
GARFI1	[75]	[104]	United States	P	1959 -	1960,	1971	153	Dur 6 mo
CHAN	[105]	[106,107]	Hong Kong	CC	1976 -	1977		84	
CORREA	[67]		United States	CC	1979 -	1982		32	
TRICHO	[27]	[108,109]	Greece	CC	1978 -	1982		77	
BUFFLE	[110]		United States	CC	1976 -	1980		52	
HIRAYA	[28]	[111-120]	Japan	P	1965 -	1966,	1981	264	
KABAT1	[53]		United States	CC	1971 -	1980		76	
GARFI2	[121]	[122]	United States	CC	1971 -	1981		134	
LAMW	[29]		Hong Kong	CC	1981 -	1984		75	
WU	[123]		United States	CC	1981 -	1982		31	
AKIBA	[68]		Japan	CC	1971 -	1980		113	
LEE	[124]		United Kingdom	CC	1979 -	1982		47	
BROWN1	[125]		United States	CC	1979 -	1982		19	
GAO	[126]		China	CC	1984 -	1986		246	
HUMBL1	[127]		United States	CC	1980 -	1984		28	Dur 6 mo
KOO	[128]	[129-133]	Hong Kong	CC	1981 -	1983		88	N20
LAMT	[30]		Hong Kong	CC	1983 -	1986		199	Occ (1 yr)
PERSHA	[134]	[135]	Sweden	CC	1961 -	1980		77	
BUTLER	[136]		United States	P	1976 -	1976,	1982	8	
GENG	[31]	[137]	China	CC	1983 -	1983		54	
INOUE	[138]		Japan	CC	1973 -	1983		28	
SHIMIZ	[70]		Japan	CC	1982 -	1985		90	
CHOI	[139]		South Korea	CC	1985 -	1988		88	
HOLE	[140]	[141]	Scotland	P	1972 -	1976,	1985	9	
SCHOEN	[142]		United States	CC	1982 -	1983		116	
SVENSS	[143]	[144]	Sweden	CC	1983 -	1985		34	Occ
JANERI	[72]	[145]	United States	CC	1982 -	1985		191	N100
KALAND	[32]		Greece	CC	1987 -	1989		91	
SOBUE	[146]	[147]	Japan	CC	1986 -	1988		144	
WU-WIL	[46]		China	CC	1985 -	1987		417	
LIUZ	[148]	[149,150]	China	CC	1985 -	1986		54	1sm
BROWN2	[151]	[152-155]	United States	CC	1986 -	1991		432	
STOCKW	[58]	[156]	United States	CC	1987 -	1991		210	N100, Dur 6 mo
DU	[52]	[157-159]	China	CC	1986 -	1986		75	
LIUQ	[160]		China	CC	1983 -	1984		38	
FONTHA	[33]	[161-164]	United States	CC	1986 -	1988		653	N100, Dur 6 mo
LAYARD	[165]		United States	CC	1986 -	1986		60	
DEWAAR	[166]	[167]	Netherlands	CC	1977 -	1991		23	Cot
KABAT2	[168]	[169,170]	United States	CC	1983 -	1990		110	
SCHWAR	[57]		United States	CC	1984 -	1987		257	
SUN	[60]		China	CC	NA			230	
WANGS	[34]		China	CC	NA			82	
WANGT	[171]		China	CC	1992 -	1994		135	
CARDEN	[73]	[172,173]	United States	P	1982 -	1982,	1989	362	
ZHENG	[35]		China	CC	1990 -	1993		94	Non
AUVINE	[174]		Finland	CC	1986 -	1992		44	
BOFFET	[66]	[175-180]	West Europe	CC	1988 -	1994		640	N400
SHEN	[181]	[182-185]	China	CC	1993 -	1993		70	
ZARIDZ	[36]	[186-188]	Russia	CC	1991 -	1993		189	
BOFFE2	[189]		Europe	CC	1994 -	1996		70	N400
JEE	[190]		South Korea	P	1992 -	1994,	1997	79	Occ, Dur 1 yr
RAPITI	[61]		India	CC	1991 -	1992		58	N400
SPEIZE	[191]		United States	P	1982 -	1982,	1992	35	
ZHONG	[54]		China	CC	1992 -	1994		504	Dur 6 mo
LEECH	[37]	[192-194]	Taiwan	CC	1992 -	1998		268	N400
MALATS	[195]	[196]	Europe/Brazil	CC	NA			122	Occ
WANGL	[62]	[197]	China	CC	1994 -	1998		233	Dur 6 mo
JOHNSO	[198]	[199-201]	Canada	CC	1994 -	1997		71	N100
LAGARD	[202]	[203]	Sweden	CC	1980 -	1995		433	Occ (1 yr)
NISHIN	[204]		Japan	P	1984 -	1984,	1992	24	
OHNO	[205]		Japan	CC	NA			191	N365
RACHTA	[63]	[206]	Poland	CC	1991 -	1997		54	Dur 6 mo
ENSTRO	[207]	[208]	United States	P	1959 -	1960,	1998	256	
ZATLOU	[64]	[209,210]	Czech Republic	CC	1998 -	2002		84	N100
IARCKR	[1]	[180]	Germany	CC	1990 -	1996		123	Dur 6 mo, N400
MCGHEE	[211]		Hong Kong	CC	1998 -	1998		324	
EPICA	[212]	[213-216]	Western Europe	P	1993 -	1998,	2000	59	

FANG	[38]	[216]	China	CC	2001 -	2004		157	
FRANCO	[71]	[216]	Mexico	CC	2000 -	2002		94	
GORLOV	[55]	[217-222]	United States	CC	1995 -	2003		193	N100
NEUBER	[49]		United States	CC	1994 -	1997		56	N100, Dur 6 mo
RYLAND	[223]		Sweden	CC	1989 -	1994		49	
WEN	[56]	[224-227]	China	P	1997 -	2000,	2004	106	
YU	[228]	[228-230]	Hong Kong	CC	2002 -	2004		213	N400, Dur 1 yr
ZEKA	[59]		East Europe, United Kingdom	CC	1998 -	2002		223	N100
HILL1	[231]		New Zealand	P	1981 -	1981,	1984	147	Occ
HILL2	[231]		New Zealand	P	1996 -	1996,	1999	234	Occ
LOPEZC	[232]		Spain	CC	2000 -	2005		36	N100
ASOMAN	[233]		United States	CC	1992 -	NA		138	Occ (1 yr)
GALLEG	[51]		Mexico	CC	2003 -	2007		32	
KURAHA	[234]		Japan	P	1990 -	1993,	2004	109	
PANDEY	[50]		Nepal	CC	NA			268	
YANG	[39]	[65,221,235,236]	United States	CC	1997 -	2008		297	N100
OLIVOM	[65]	[237]	United States	CC	NA			45	N100
TSE	[238]	[239]	China	CC	2004 -	2006		132	N400, Dur 1 yr
LIANG	[40]		China	CC	2004 -	2007		226	
BRENNE	[47]		Canada	CC	1997 -	2002		156	N100
JIANG	[41]		China	CC	2009 -	2009		145	
EPICC	[240]	[212]	Western Europe	P	1992 -	1998,	2006	98	
KIYOHA	[241]		Japan	CC	1996 -	2008		153	
HE	[242]	[243]	China	P	1976 -	1994,	2011	16	N100
LIM	[74]	[244-246]	China	CC	1996 -	2008		433	Occ (1 yr)
LIN	[42]		China	CC	2006 -	2010		226	
FERREC	[247]		Chile	CC	2007 -	2010		59	
ALZOUG	[48]	[248,249]	Canada	CC	1996 -	2000		44	N100
GELAC	[43]		Taiwan	CC	2002 -	2009		1540	Occ
MASJED	[44]	[250]	Iran	CC	2002 -	2005		81	Dur 6 mo
REN	[251]		China	CC	2002 -	2012		764	
SEKI	[252]		Japan	CC	1997 -	2009		431	
WHIOS	[253]	[254]	United States	P	1993 -	1998,	2009	200	
ILCCO	[45]	[69]	International	CC	1984 -	2014		2504	N100
TORRES	[255]	[256]	Spain	CC	2011 -	2013		192	N100

[1]Study design is coded as P: Prospective; CC: Case control; [2]Study dates are given as Start year, End year, Final follow-up year (prospective studies only); [3]Inclusion of "near equivalents" to never smokers, coded as Dur: Includes those who smoked up to a number of months (mo) or years (yr); N: Includes those who smoked up to a number of cigarettes in their lifetime; Occ: Includes occasional smokers; Occ (1 yr): Includes those who smoked occasionally for up to 1 year; Non: Described as "non-smokers" and assumed from context to mean never smokers; 1sm: Study included 1 smoker; Cot: Excluded self-reported never smokers with urinary cotinine > 100 ng/mg.

Table 2 Further details of the 102 studies

Ref.	ETS exposures[1]	Adjustment variables used[2]	Extent (%) of histological confirmation	Results by histological type	Dose-response results available[3]
GARFI1	s	7	NA		Yes
CHAN	s	0	80		
CORREA	s c[4]	1	97		Yes
TRICHO	s	0	27	Yes	Yes
BUFFLE	h	0	100		Yes
HIRAYA	s	2	NA		Yes
KABAT1	s h w	4	100		
GARFI2	s h w c o tot	4	100	Yes	Yes
LAMW	s tot	1	100	Yes	
WU	s w c tot[4]	2	100	Yes	
AKIBA	s c	6	53		Yes
LEE	s h w tr o tot	3	38	Yes	
BROWN1	tot	3	100	Yes	
GAO	s h c tot	2	43		Yes
HUMBL1	s	2	100		Yes
KOO	s h w c tot	5	97	Yes	Yes
LAMT	s	0	100	Yes	Yes
PERSHA	s c	2	83	Yes	Yes
BUTLER	s	2	100		
GENG	s	0	85		Yes
INOUE	s	3	NA		Yes
SHIMIZ	s h w	3	100		
CHOI	s	0	100		Yes

HOLE	h	2	NA		Yes
SCHOEN	s	6	100		
SVENSS	h c tot	1	70		
JANERI	s h w c o	3	100	Yes	Yes
KALAND	s h w	5	48	Yes	Yes
SOBUE	s h c	3	100		
WU-WIL	s h w c	5	42		
LIUZ	h	3	17		
BROWN2	s h w c	2	76	Yes	Yes
STOCKW	s h w[4] c o[4] tot	3	100	Yes	Yes
DU	s	2	NA		Yes
LIUQ	s	3	32		Yes
FONTHA	s h w c o tot	10	100	Yes	Yes
LAYARD	s	3	NA		Yes
DEWAAR	tot	0	71		Yes
KABAT2	s h w c tr o tot	6	100		Yes
SCHWAR	h w	2	100		
SUN	s h w c hw tot	2	100	Yes	
WANGS	tot	0	100		
WANGT	s w c	1	57		Yes
CARDEN	s h w o tot	8	NA		Yes
ZHENG	h	2	82	Yes	Yes
AUVINE	tot	1	NA		
BOFFET	s h w c tr o tot	7	96	Yes	Yes
SHEN	tot	9	100	Yes	Yes
ZARIDZ	s h w c	2	100	Yes	Yes
BOFFE2	s w c tot	5	100	Yes	Yes
JEE	s	5	0		Yes
RAPITI	s w c tr	3	100	Yes	Yes
SPEIZE	tot	1	100		
ZHONG	s h w c tot	7	57	Yes	Yes
LEECH	s h w c tot	7	100		Yes
MALATS	s tot	2	100		Yes
WANGL	h c	6	32		Yes
JOHNSO	h w c tot	4	100		Yes
LAGARD	h tot	6	100		
NISHIN	s h	7	NA		
OHNO	s w c tr o tot	2	100		Yes
RACHTA	c	21	100	Yes	
ENSTRO	s	8	NA		
ZATLOU	c tot	3	100	Yes	
IARCKR	s w c	2	100		Yes
MCGHEE	h	2	0		Yes
EPICA	h w tot	7	NA		
FANG	tot	8	100		Yes
FRANCO	h	2	100		
GORLOV	h w hw tot	4	100		
NEUBER	tot[4]	3	100		
RYLAND	h w	3	98		
WEN	s w c tot	9	NA		Yes
YU	tot	20	100		Yes
ZEKA	w	4	NA		Yes
HILL1	h	9	NA		
HILL2	h	9	NA		
LOPEZC	tot	0	100		
ASOMAN	h w o	0	100		
GALLEG	tot	0	100		
KURAHA	s w c hw tot	5	90	Yes	Yes
PANDEY	c tot	0	NA		Yes
YANG	c tot	5	NA		
OLIVOM	c	4	100	Yes	
TSE	h w tot	9	100	Yes	Yes
LIANG	c tot	0	100		
BRENNE	h w c tot	3	100		Yes
JIANG	tot	17	100	Yes	
EPICC	c	10	NA		Yes
KIYOHA	s	0	100		
HE	tot	9	88		Yes
LIM	h	0	96		
LIN	tot	9	100		Yes
FERREC	c tot[4]	3	72		

ALZOUG	s h w c tot	3	NA	Yes	Yes
GELAC	s h w hw tot	6	100		Yes
MASJED	s h w o tot	4	100	Yes	
REN	tot	5	100		
SEKI	s	7	94	Yes	
WHIOS	h4 w[4] c[4] tot	0	0		[4]
ILCCO	h w c tot	3	100	Yes	Yes
TORRES	h	2	99		Yes

[1]ETS exposure measures reported, coded as s: Spousal; h: Household; w: Work; c: Childhood; hw: Exposure at both home and work; tr: Travel; o: Social/other; tot: Total exposure. Codes marked 4 represent exposures for which the only result presented is a statement that no association was found; [2]Number of factors adjusted for, excluding sex; [3]Coded as yes: Dose response result presented; [4]The only dose response result presented is a statement that no dose response was found. NA: Not available.

study found no association. One study[52] reported ETS was not statistically associated with lung cancer, but gave no further details and could not be included in the meta-analysis. Heterogeneity between studies was not significant, and fixed-effect (1.15, 1.03-1.28) and random-effects estimates (1.14, 1.01-1.29) were similar. There was no evidence of publication bias (P > 0.1).

Results by sex, separated by region, are given as forest plots in Figure 1 (husband smoking) and Figure 2 (wife smoking).

Further meta-analyses were carried out on results for smoking by either the husband or the wife (or nearest equivalent), based on 119 RR estimates. Details are given in Table 3, along with estimates split by various other factors. Overall, a fixed-effect RR (1.18, 1.14-1.23) and a random-effects RR (1.21, 1.14-1.29) were estimated, with marked heterogeneity between studies (P < 0.001). When the studies were examined according to various factors, there was evidence of heterogeneity between factor levels for publication date (P < 0.01), study size (P < 0.01) and age adjustment (P < 0.05), with the largest RRs seen for early (1981-1989) studies, small studies (1-49 cases) and estimates unadjusted for age. There was no significant heterogeneity by location, study type, reporting of dose-response results, or use of spouse as the index of exposure. There was no clear evidence of publication bias (0.05 < P < 0.1).

Results for smoking by the spouse (or nearest equivalent) were also examined by histological type of cancer, with Figure 3 (squamous cell carcinoma) and Figure 4 (adenocarcinoma) showing forest plots by region. The analysis of squamous cell carcinoma, based on 24 RR estimates, showed a significant (P < 0.001) positive association and heterogeneity (P < 0.001), overall estimates being 1.41 (1.24-1.59, fixed-effect) and 1.44 (1.15-1.80, random-effects). No significant variation by region was seen. For adenocarcinoma, the 30 RR estimates were again heterogeneous (P < 0.01), with the meta-analysis showing significantly raised RRs, of 1.23 (1.15-1.32, fixed-effect) and 1.33 (1.17-1.51, random-effects). The heterogeneity was partly due to differences (P < 0.001) by region, with little increase seen in North American and European studies (random-effects RRs 1.08, 0.96-1.22 for North America; 1.11, 0.82-1.49 for Europe), but a clear increase for Asia (random-effects RR 1.70, 1.35-2.15).

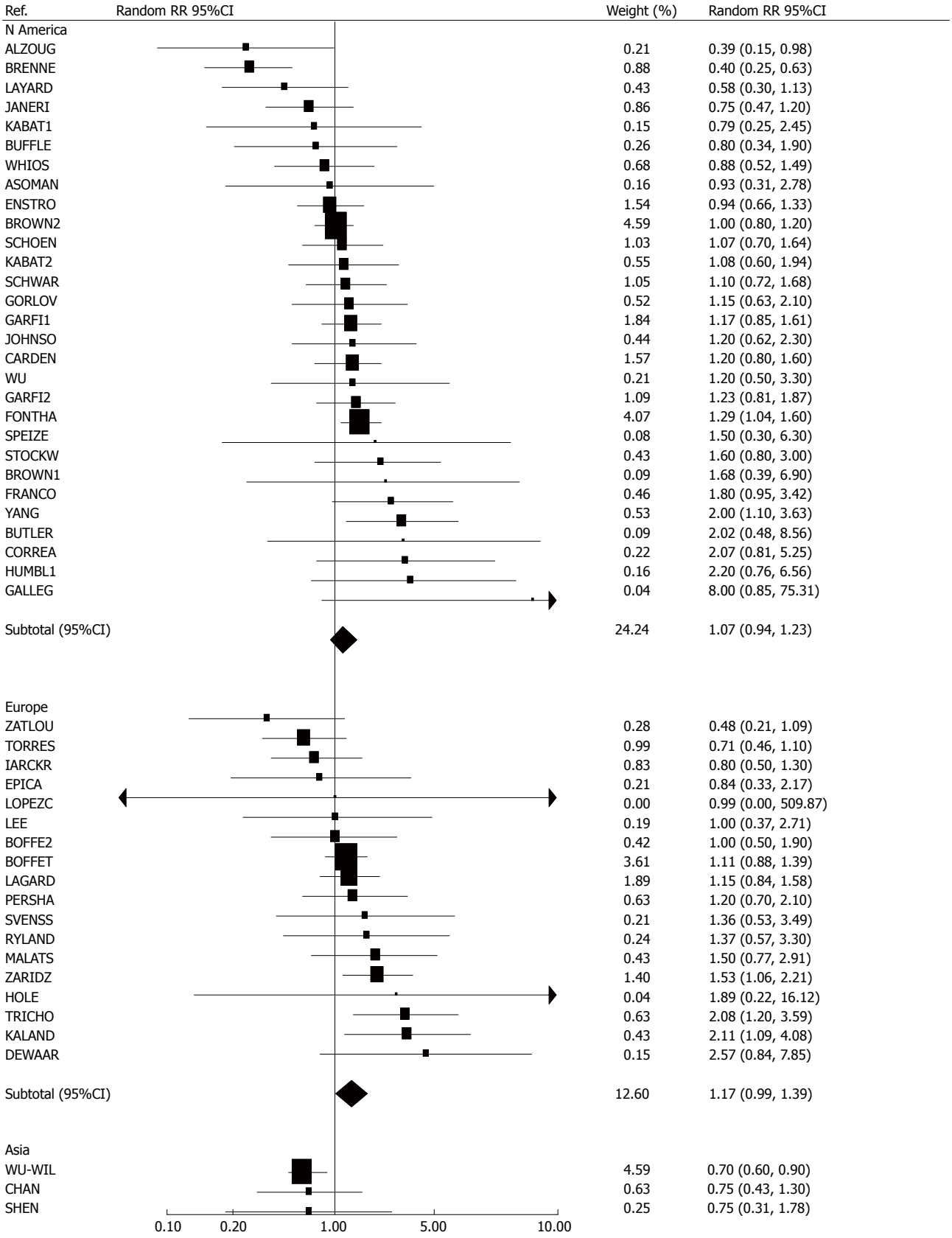
Workplace ETS exposure

For lung cancer and workplace ETS exposure, 47 RR estimates were available (Figure 5). Of these, 37 were raised, with estimates from six studies[33,45,53-56] being significant, and another[57] of borderline significance. This contrasted with nine studies, where RRs were non-significantly below 1.00, and one showing no association. Two other studies[58,59], neither of which reported an association, could not be included in the meta-analysis, due to providing insufficient detail. Overall, there was a significant positive relationship, whether based on fixed-effect (1.21, 1.14-1.28) or random-effects RRs (1.22, 1.15-1.30). There was no evidence of heterogeneity or publication bias. Studies conducted in North America (1.21, 1.08-1.37), Europe (1.18, 1.01-1.39) and Asia (1.33, 1.20-1.47) all showed a significantly increased random-effects RR.

Childhood ETS exposure

Results for childhood ETS exposure are given, by region, in Figure 6, with further meta-analyses given in Table 4. For childhood exposure from any cohabitant, 41 RR estimates were available. Of these, 21 were raised, eight significantly[37,39,60-65]. In contrast 18 RR estimates were below 1.00, one[66] significantly so, while two were equal to 1.00. In addition, three studies[67-69] found no relationship but provided insufficient detail for inclusion in the meta-analysis. Although meta-analysis suggested a positive relationship with the risk of lung cancer, this only just reached statistical significance (fixed-effect RR = 1.08, 1.01-1.15; random-effects RR = 1.15, 1.02-1.29). There was significant heterogeneity between the studies (P < 0.001), and heterogeneity between the continents (P < 0.05), with a significant increase seen in Asia (random-effects RR = 1.31, 1.02-1.67), but not in North America (RR = 1.06, 0.89-1.28) or Europe (RR = 1.02, 0.81-1.29).

Based on nine RR estimates, meta-analysis showed no evidence of any relationship specifically with maternal smoking in childhood, with the fixed-effect estimate 0.96 (0.77-1.20) and the random-effects estimate 0.98 (0.77-1.25). There was also no association specifically with paternal smoking in childhood (fixed-effect model


Ref.
Random RR 95%CI
Weight (%)
Random RR 95%CI
N America
ALZOUG 0.21 0.39 (0.15, 0.98)
BRENNE 0.88 0.40 (0.25, 0.63)
LAYARD 0.43 0.58 (0.30, 1.13)
JANERI 0.86 0.75 (0.47, 1.20)
KABAT1 0.15 0.79 (0.25, 2.45)
BUFFLE 0.26 0.80 (0.34, 1.90)
WHIOS 0.68 0.88 (0.52, 1.49)
ASOMAN 0.16 0.93 (0.31, 2.78)
ENSTRO 1.54 0.94 (0.66, 1.33)
BROWN2 4.59 1.00 (0.80, 1.20)
SCHOEN 1.03 1.07 (0.70, 1.64)
KABAT2 0.55 1.08 (0.60, 1.94)
SCHWAR 1.05 1.10 (0.72, 1.68)
GORLOV 0.52 1.15 (0.63, 2.10)
GARFI1 1.84 1.17 (0.85, 1.61)
JOHNSO 0.44 1.20 (0.62, 2.30)
CARDEN 1.57 1.20 (0.80, 1.60)
WU 0.21 1.20 (0.50, 3.30)
GARFI2 1.09 1.23 (0.81, 1.87)
FONTHA 4.07 1.29 (1.04, 1.60)
SPEIZE 0.08 1.50 (0.30, 6.30)
STOCKW 0.43 1.60 (0.80, 3.00)
BROWN1 0.09 1.68 (0.39, 6.90)
FRANCO 0.46 1.80 (0.95, 3.42)
YANG 0.53 2.00 (1.10, 3.63)
BUTLER 0.09 2.02 (0.48, 8.56)
CORREA 0.22 2.07 (0.81, 5.25)
HUMBL1 0.16 2.20 (0.76, 6.56)
GALLEG 0.04 8.00 (0.85, 75.31)
Subtotal (95%CI) 24.24 1.07 (0.94, 1.23)
Europe
ZATLOU 0.28 0.48 (0.21, 1.09)
TORRES 0.99 0.71 (0.46, 1.10)
IARCKR 0.83 0.80 (0.50, 1.30)
EPICA 0.21 0.84 (0.33, 2.17)
LOPEZC 0.00 0.99 (0.00, 509.87)
LEE 0.19 1.00 (0.37, 2.71)
BOFFE2 0.42 1.00 (0.50, 1.90)
BOFFET 3.61 1.11 (0.88, 1.39)
LAGARD 1.89 1.15 (0.84, 1.58)
PERSHA 0.63 1.20 (0.70, 2.10)
SVENSS 0.21 1.36 (0.53, 3.49)
RYLAND 0.24 1.37 (0.57, 3.30)
MALATS 0.43 1.50 (0.77, 2.91)
ZARIDZ 1.40 1.53 (1.06, 2.21)
HOLE 0.04 1.89 (0.22, 16.12)
TRICHO 0.63 2.08 (1.20, 3.59)
KALAND 0.43 2.11 (1.09, 4.08)
DEWAAR 0.15 2.57 (0.84, 7.85)
Subtotal (95%CI) 12.60 1.17 (0.99, 1.39)
Asia
WU-WIL 4.59 0.70 (0.60, 0.90)
CHAN 0.63 0.75 (0.43, 1.30)
SHEN 0.25 0.75 (0.31, 1.78)
0.10
0.20
1.00
5.00
10.00

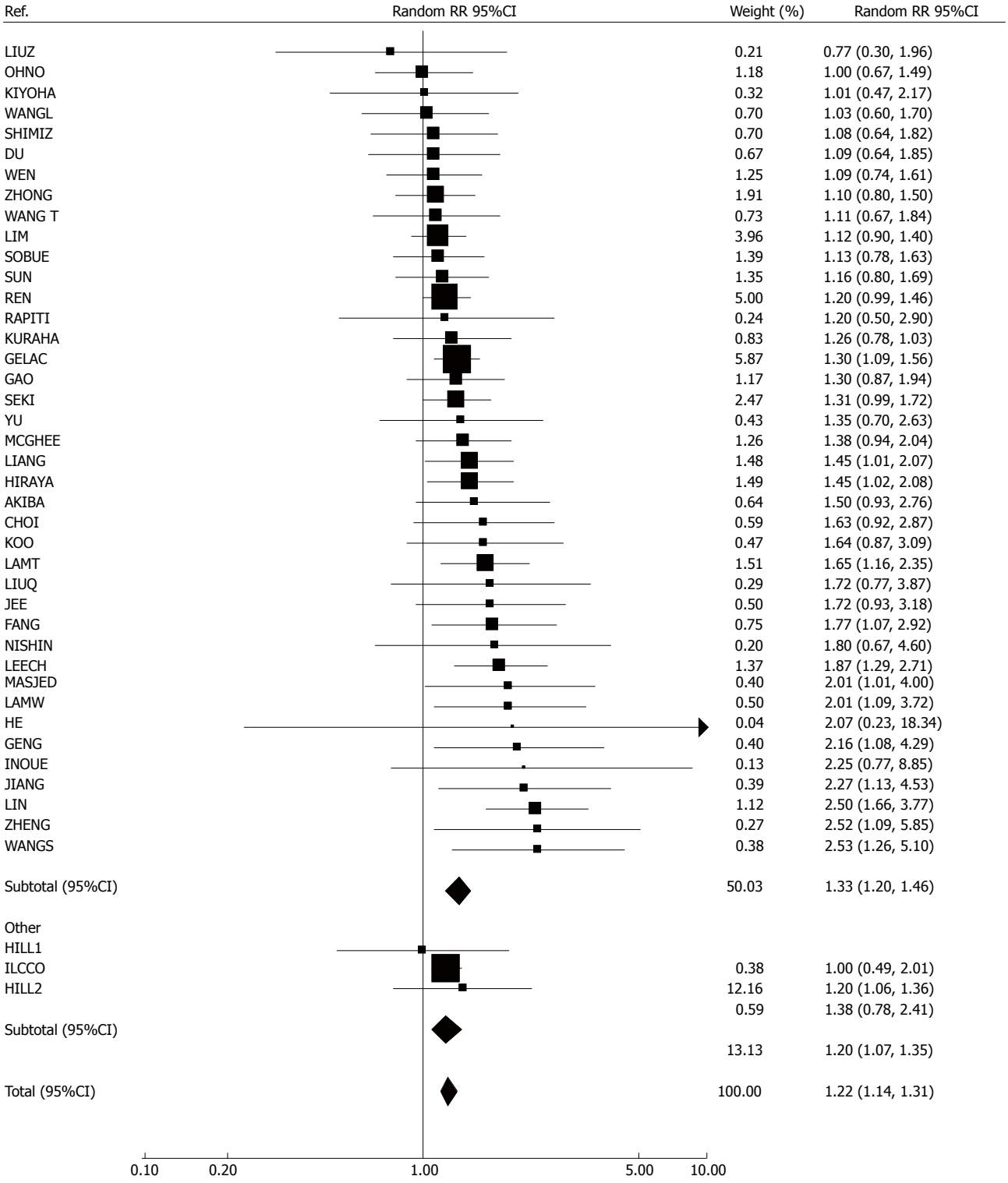


Figure 1 Forest plots for smoking by husband, by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk

0.90, 0.80-1.00; random-effects model 1.00, 0.78-1.29), based on 11 estimates. However, meta-analysis of the eight estimates specifically considering parental smoking during childhood gave a reduced RR (0.78, 0.64-0.94 for both models). There was no significant heterogeneity for maternal smoking or parental smoking, but there was for paternal smoking ($P < 0.001$) due to an atypically high estimate of 12.64 (4.89-32.68) for females in one study[61].

None of the analyses of childhood exposure showed any significant evidence of publication bias.

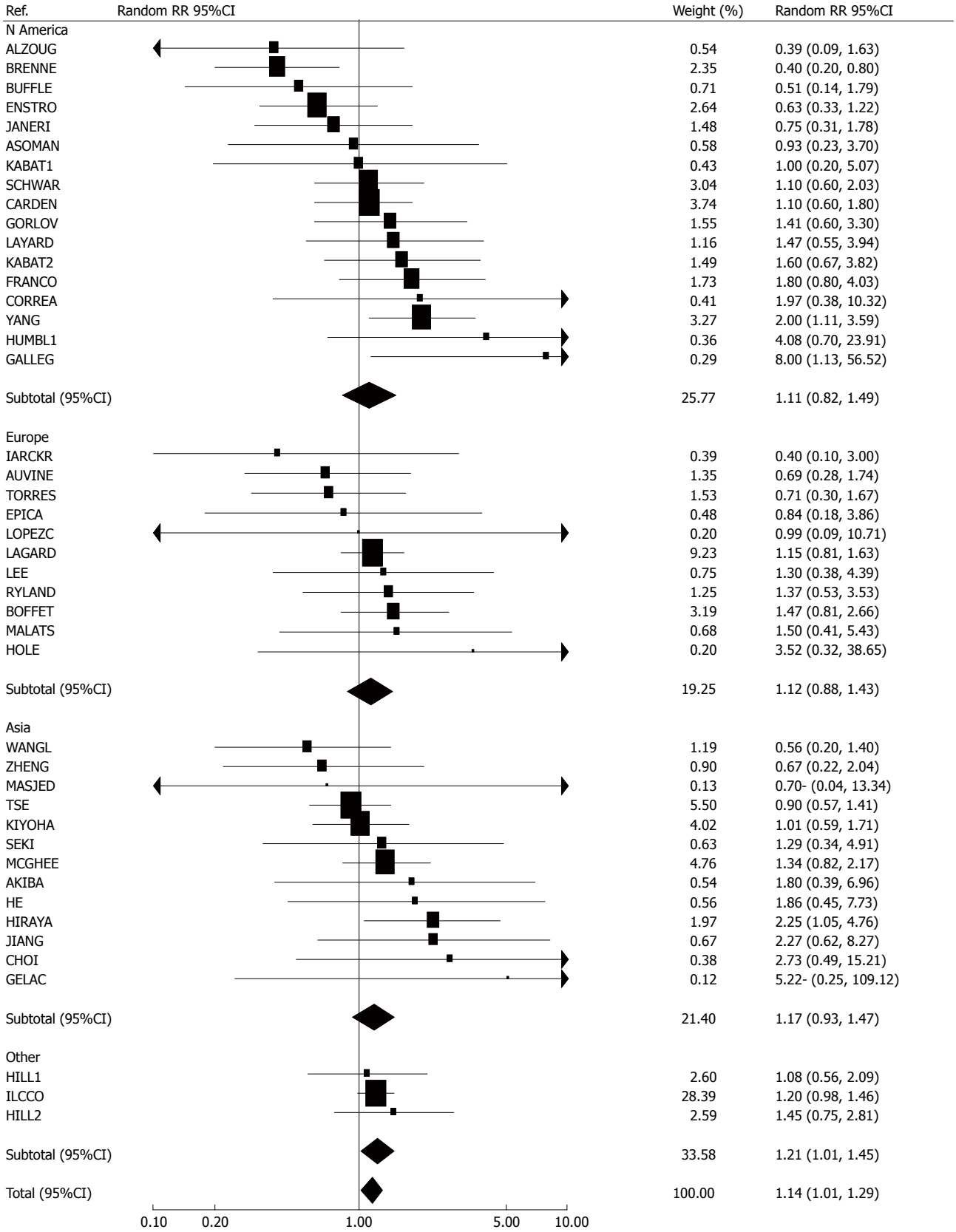


Figure 2 Forest plots for smoking by wife, by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a ~ are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

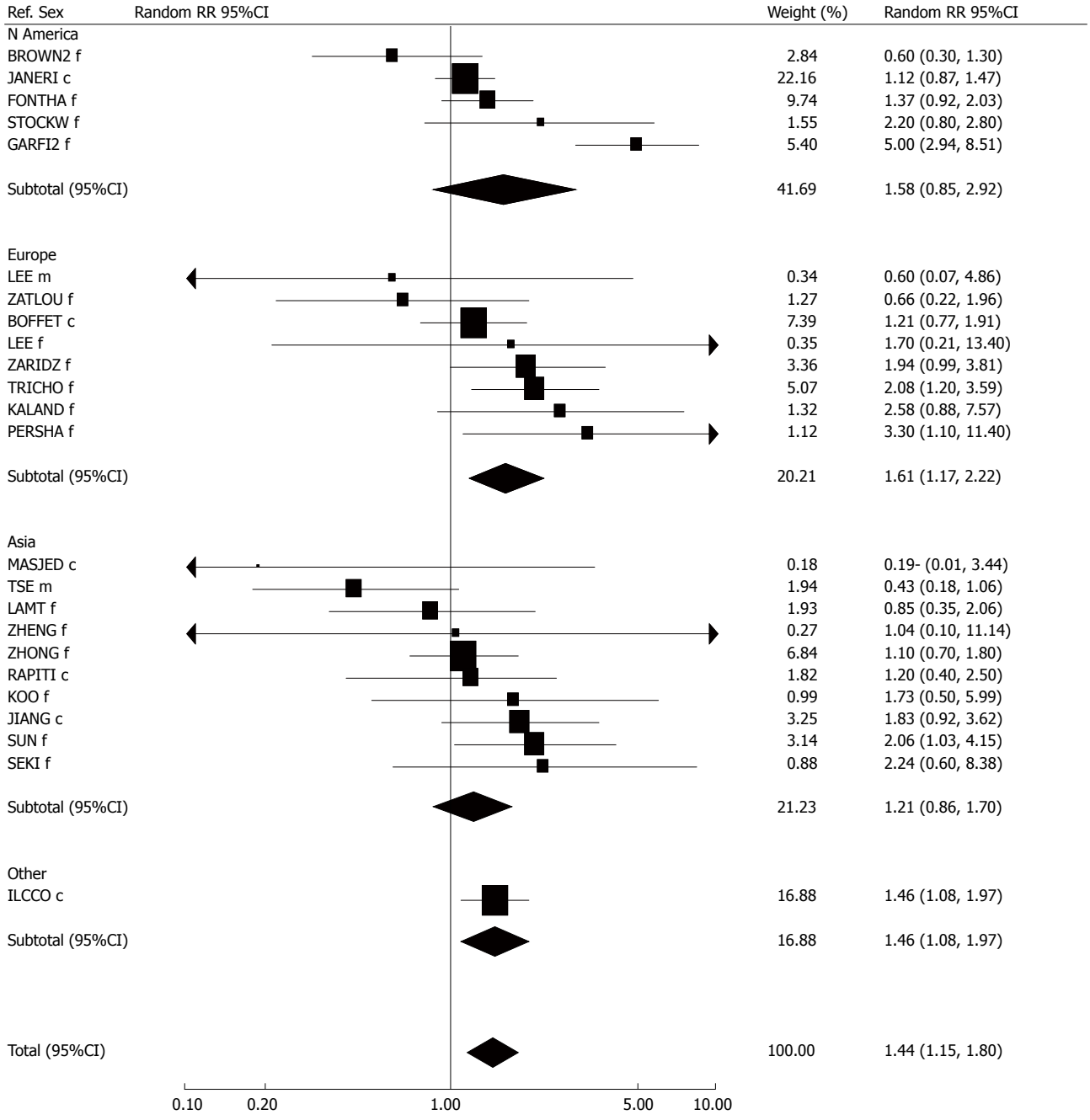


Figure 3 Forest plots for squamous cell carcinoma and spousal smoking, by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

Household ETS exposure

A total of 58 RR estimates were available for household ETS exposure from any source, as shown in Figure 7. Thirty-six RRs were above 1.00, statistically significant in six studies[35,43,45,60,70,71]. Twenty-one non-significantly negative RRs were also reported, while one study found no association. Overall RRs were 1.13 (1.07-1.19, fixed-effect) and 1.11 (1.05-1.18, random-effects). There was marked heterogeneity ($P < 0.001$) between the estimates, but no significant variation by study location, or evidence of publication bias.

Restricting attention to sources of ETS other than the spouse, only 13 RRs were available, and the overall RR, although raised, was not significant (1.04, 0.89-1.21, fixed-effect) or (1.12, 0.87-1.44, random-effects).

ETS exposure during travel

Figure 8 shows the eight RRs for ETS exposure during travel. Six were above 1.00, and two were below 1.00. Only one estimate[61] was significant, and its high RR of

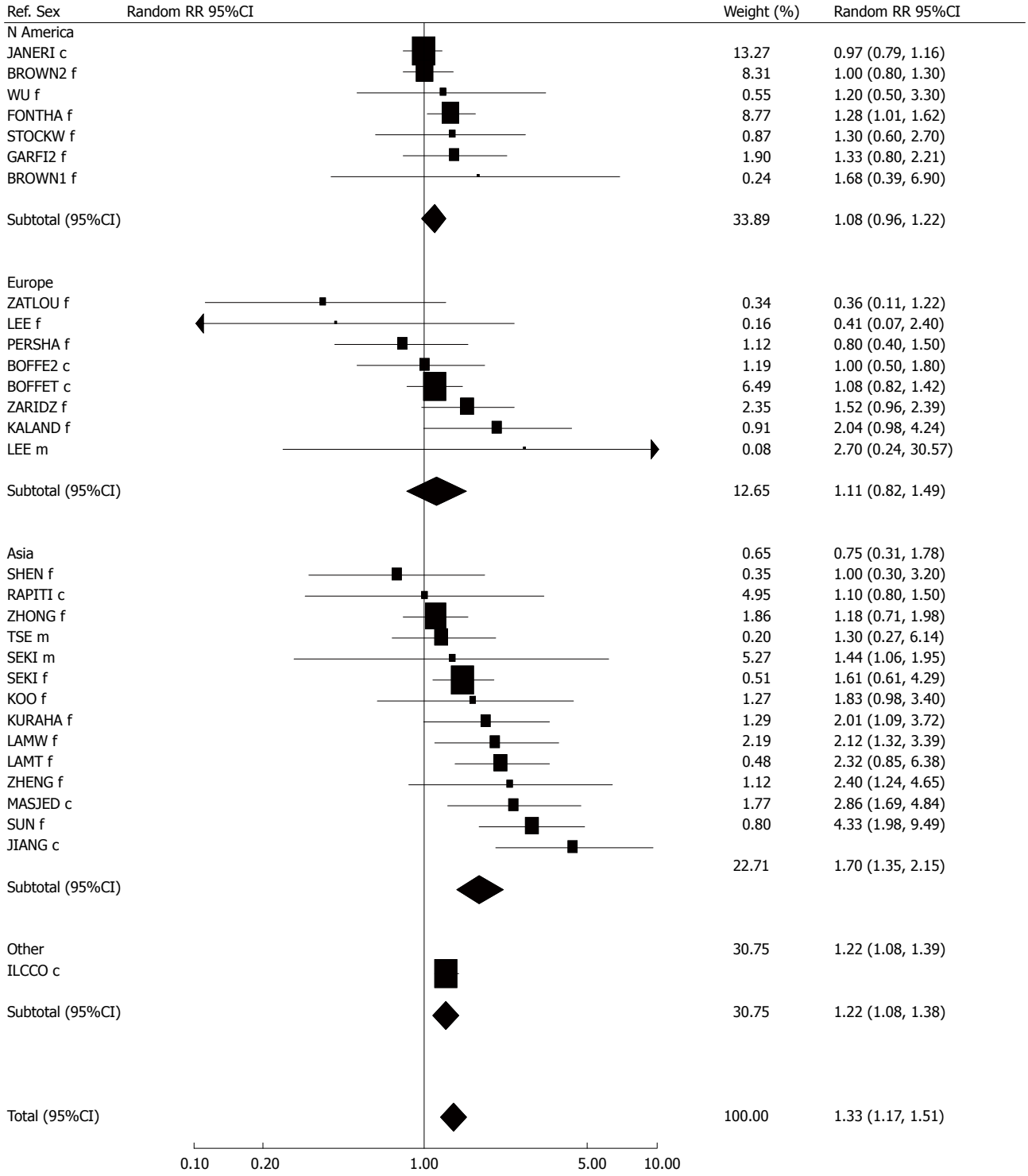


Figure 4 Forest plots for adenocarcinoma and spousal smoking, by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

5.20 was the major contributor to the significant (P < 0.05) heterogeneity. Fixed effect meta-analysis gave a RR which was just significant (1.24, 1.01-1.53), but the random-effects RR was not (1.34, 0.94-1.93).

ETS exposure in social situations

Analysis of the relationship of lung cancer to ETS exposure in social situations was based on 15 RR estimates, shown in Figure 9. One[33] study provided a significantly increased

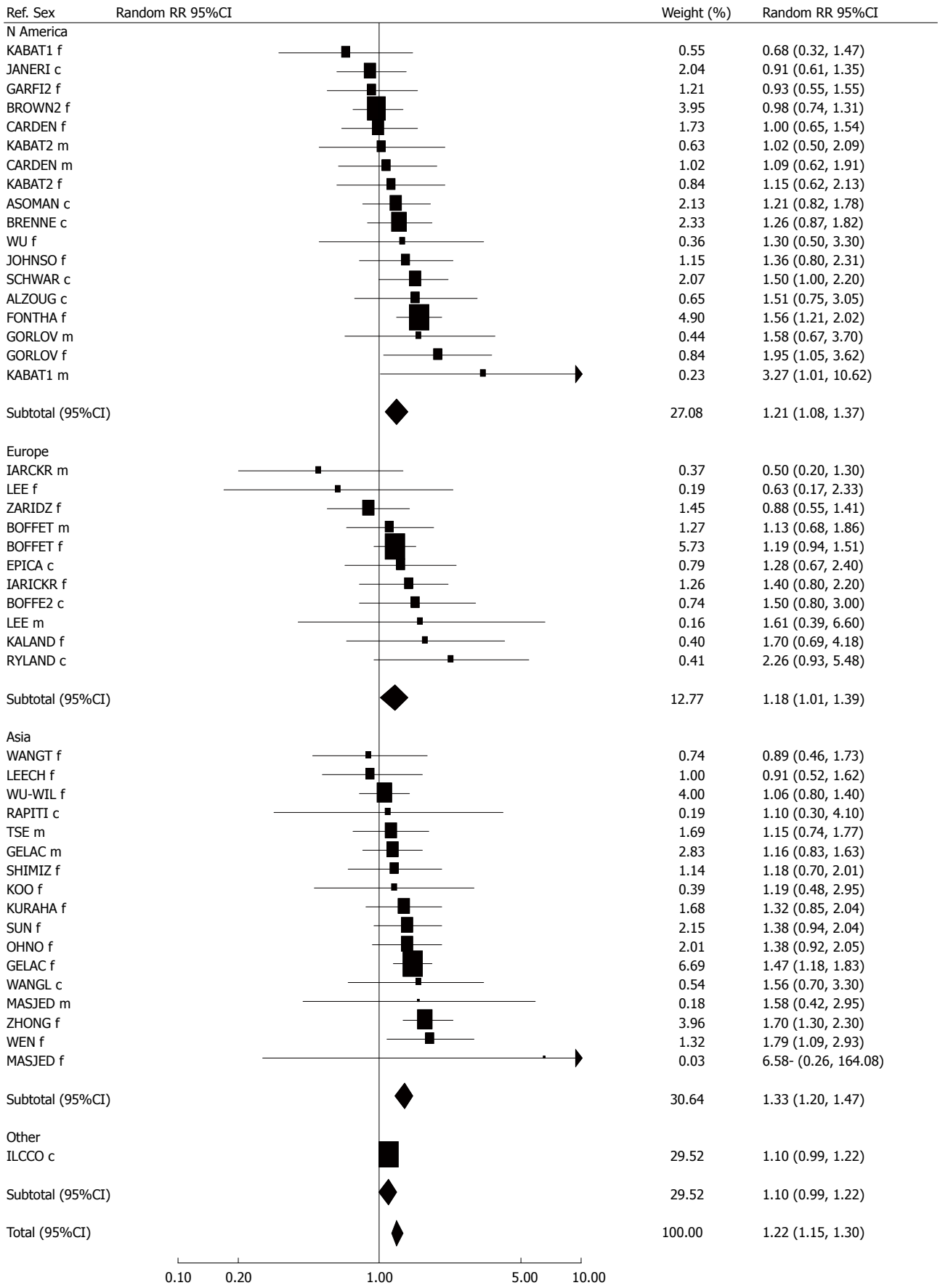


Figure 5 Forest plots for workplace environmental tobacco smoke exposure by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

Table 3 Meta-analyses of smoking by the spouse (or nearest equivalent)

Estimates considered	No. of estimates	Relative risk (95% confidence limits)		Heterogeneity[1]
		Fixed-effects meta-analysis	Random-effects meta-analysis	
All	119	1.18 (1.14-1.23)	1.21 (1.14-1.29)	+++
N America	38	1.08 (1.00-1.17)	1.09 (0.95-1.26)	+++
Europe	22	1.15 (1.03-1.28)	1.16 (1.00-1.35)	(+)
Asia	54	1.24 (1.17-1.32)	1.31 (1.20-1.44)	+++
Asia - Japan	13	1.26 (1.11-1.45)	1.26 (1.11-1.45)	NS
Asia - Hong Kong	8	1.32 (1.12-1.57)	1.31 (1.06-1.63)	NS
Asia - China	23	1.16 (1.06-1.27)	1.29 (1.08-1.54)	+++
Asia - Other	10	1.34 (1.19-1.51)	1.37 (1.19-1.57)	NS
Heterogeneity between Asian countries				NS
Other continents	5	1.20 (1.09-1.33)	1.20 (1.09-1.33)	NS
Heterogeneity between continents				(+)
Published in 1981-1989	34	1.38 (1.24-1.54)	1.38 (1.24-1.54)	NS
Published in 1990-1999	33	1.09 (1.01-1.17)	1.15 (1.02-1.28)	++
Published in 2000-2009	34	1.22 (1.12-1.33)	1.21 (1.08-1.36)	+
Published in 2010 onwards	18	1.17 (1.10-1.26)	1.13 (0.94-1.36)	+++
Heterogeneity by publication date				++
1-49 cases	23	1.44 (1.14-1.81)	1.47 (1.15-1.88)	NS
50-99	31	1.30 (1.14-1.47)	1.27 (1.08-1.50)	+
100-199	29	1.09 (1.00-1.19)	1.10 (0.96-1.26)	+++
200-399	22	1.33 (1.21-1.46)	1.32 (1.16-1.50)	+
400+	14	1.14 (1.07-1.20)	1.13 (1.02-1.25)	++
Heterogeneity by study size				++
Case-control	97	1.18 (1.13-1.23)	1.22 (1.13-1.31)	+++
Prospective	22	1.18 (1.05-1.33)	1.18 (1.05-1.33)	NS
Heterogeneity by study type				NS
Not age adjusted	21	1.34 (1.19-1.50)	1.42 (1.18-1.71)	+
Age adjusted	98	1.16 (1.11-1.21)	1.18 (1.10-1.26)	+++
Heterogeneity by age adjustment				NS
Dose-response results not reported	46	1.13 (1.06-1.21)	1.18 (1.06-1.31)	++
Only no dose-response stated	2	0.95 (0.60-1.50)	0.95 (0.60-1.50)	NS
Dose-response results reported	71	1.21 (1.15-1.28)	1.24 (1.14-1.35)	+++
Heterogeneity by dose response reporting				NS
Spouse the index	71	1.18 (1.11-1.24)	1.21 (1.12-1.31)	++
Spouse not the index	48	1.19 (1.12-1.27)	1.20 (1.07-1.35)	+++
Heterogeneity by index definition				NS

[1]Significance levels indicated by +++ $P < 0.001$, ++ $P < 0.01$, + $P < 0.05$, (+) $P < 0.1$ for heterogeneity within level and for heterogeneity between level. NS: Not significant, $P \geqslant 0.1$.

RR, with seven studies giving non-significantly raised estimates. Seven RRs were below 1.00, significantly so in two[72,73] studies. Overall, there was no evidence of an increased risk, for either fixed-effect (1.03, 0.92-1.16) or random-effects RRs (1.01, 0.82-1.24).

Total ETS exposure

The 48 RRs for total ETS exposure are shown, by region, in Figure 10. Thirty-eight were above 1.00, significantly so for 12 studies[29,34,37-39,41-43,45,51,55,60]. Eight non-significantly reduced RRs were also reported, while two studies reported RRs of 1.00. Although there was marked heterogeneity ($P < 0.001$), fixed-effect RRs (1.30, 1.22-1.38), and random-effects RRs were quite similar (1.31, 1.19-1.45). Heterogeneity between the continents was statistically significant ($P < 0.01$), with random-effects RRs higher for Asia (1.51, 1.31-1.74), than for North America (1.22, 0.96-1.55) or Europe (1.09, 0.91-1.31). There was no evidence ($P > 0.1$) of publication bias.

Smoking by the husband - detailed analyses

Smoking by the husband (or nearest equivalent) is now considered in more detail, with results presented both for overall exposure and per 10 cigarettes per day smoked by the husband. A fuller report which includes adjustment for confounding and for misclassification of exposure, is available in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf, with only the main findings presented here.

For overall exposure, the RRs considered are those shown in Figure 1 and briefly referred to in the section "smoking by the spouse". As noted there, combining estimates from 93 studies gave (RR = 1.19, 95%CI: 1.14-1.24, fixed-effects) and (RR =1.22, 95%CI: 1.14-1.31, random-effects).

Of the 93 studies, 29 were in North America, 18 in Europe, 26 in China or Hong Kong, 18 in the rest of Asia, and two in New Zealand. One Asian study[74] was of Chinese women in Singapore, and has been included in the subset of China studies. As the studies in New

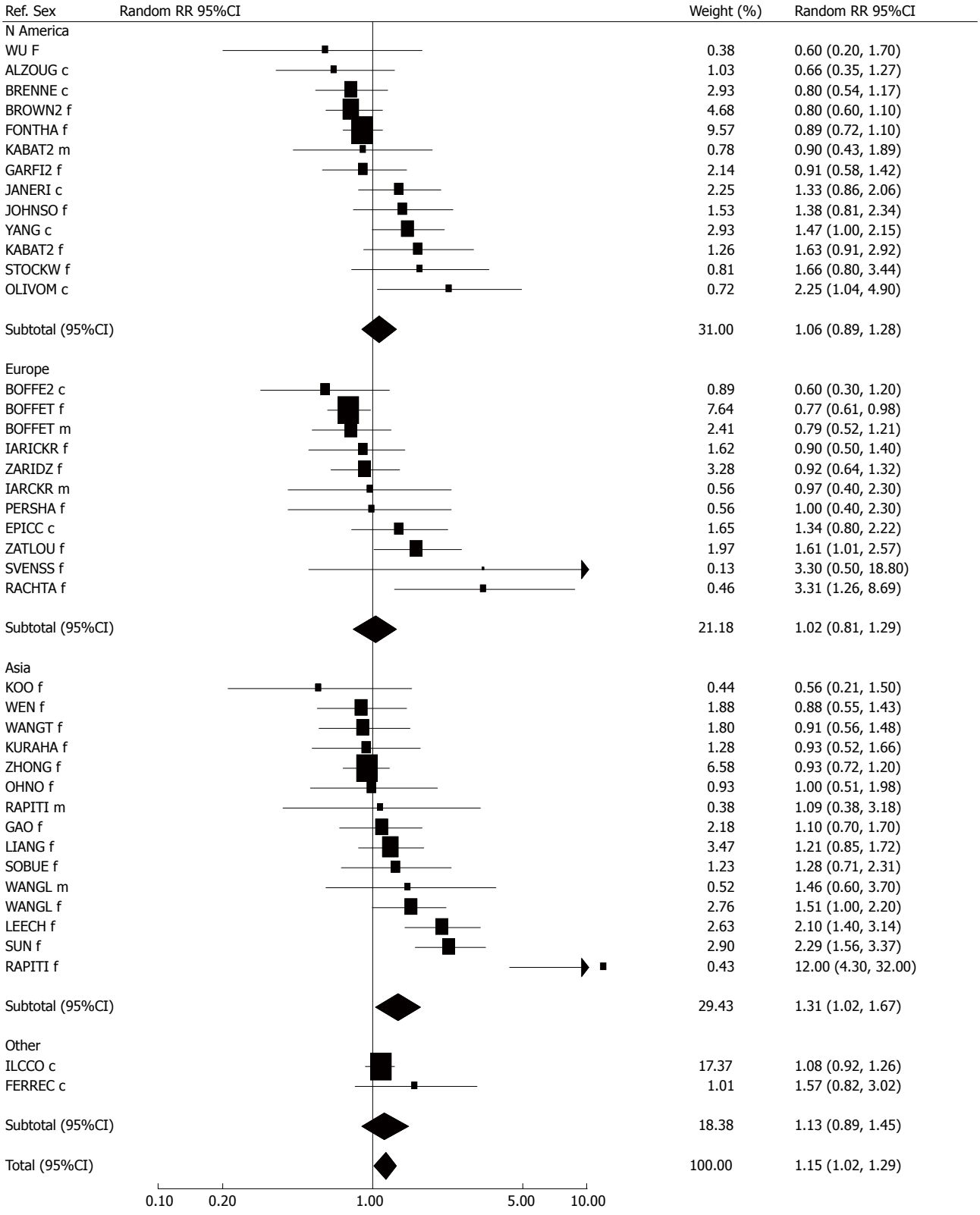


Figure 6 Forest plots for childhood environmental tobacco smoke exposure by region. Estimates of the random-effects RR and its 95%CI are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

Zealand were principally of people of European descent, they have been included in the European subset of studies. One of the studies[45] was international, but due to a high proportion of Asian subjects has been included in the Rest of Asia subset.

The first study appeared in 1981[75], a further

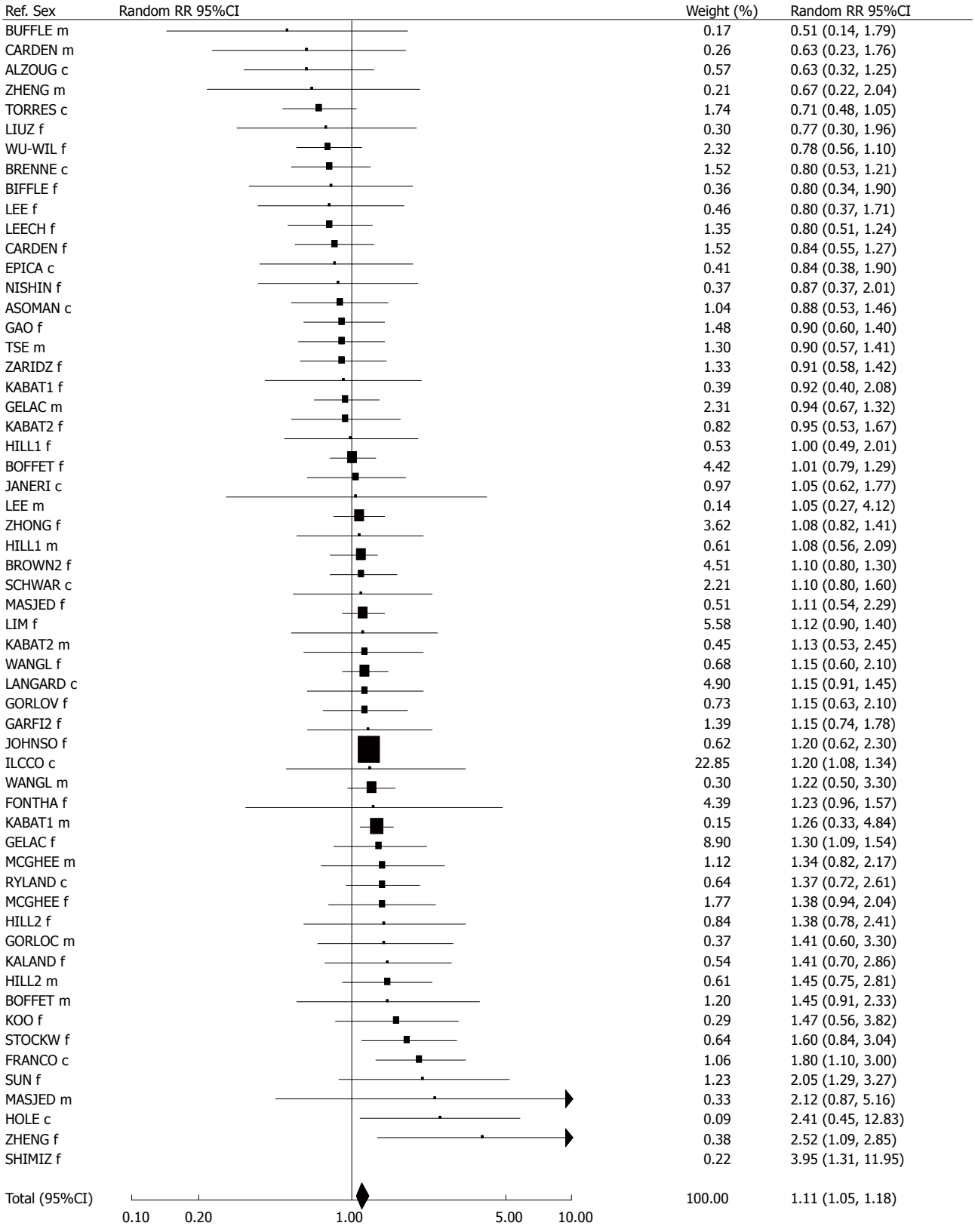


Figure 7 Forest plot for household environmental tobacco smoke exposure. Estimates of the random-effects RR and its 95%CI are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%CIs and weights are also shown. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

25, 27, 26 and 14 being published in, respectively, 1982-89, 1990-99, 2000-09 and 2010-2014. Sixteen

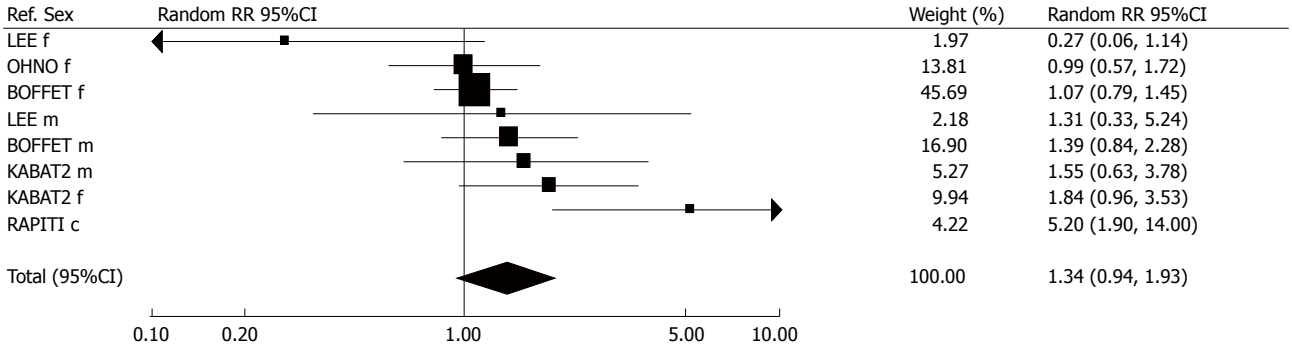


Figure 8 Forest plot for exposure to environmental tobacco smoke during travel. Estimates of the random-effects RR and its 95%CI are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%CIs and weights are also shown. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

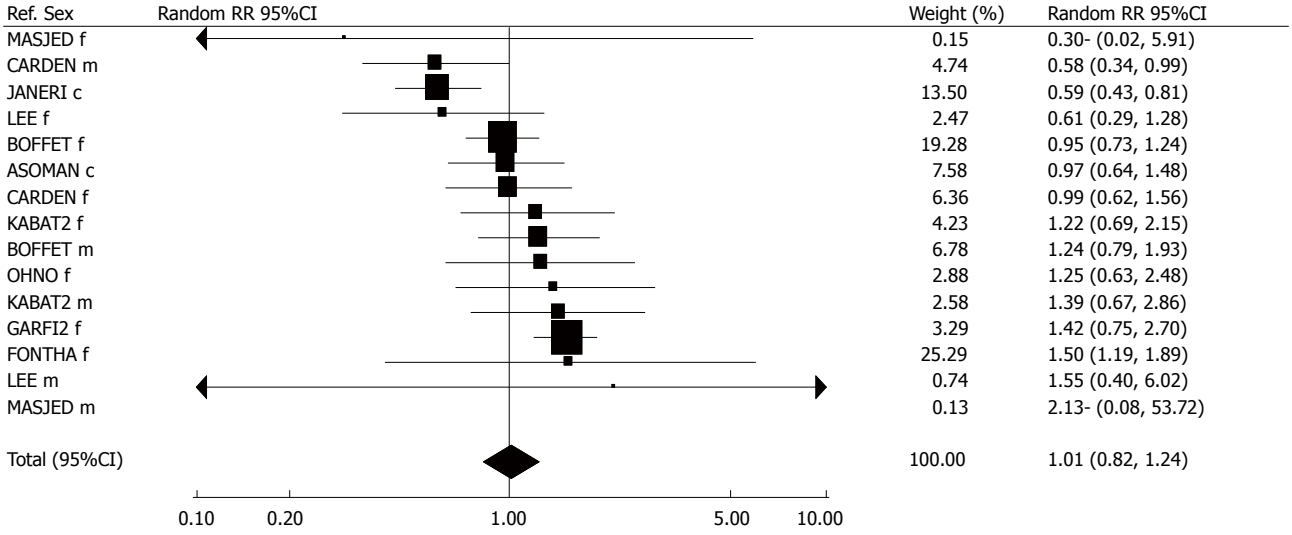


Figure 9 Forest plot for social environmental tobacco smoke exposure. Estimates of the random-effects RR and its 95%CI are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%CIs and weights are also shown. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

Table 4 Meta-analyses of childhood environmental tobacco smoke exposure

Estimates considered	No. of estimates	Relative risk (95% confidence limits)		Heterogeneity[1]
		Fixed-effects meta-analysis	Random-effects meta-analysis	
From any cohabitant	41	1.08 (1.01-1.15)	1.15 (1.02-1.29)	+++
N America	13	1.00 (0.89-1.13)	1.06 (0.89-1.28)	+
Europe	11	0.94 (0.81-1.08)	1.02 (0.81-1.29)	+
Asia	15	1.26 (1.11-1.42)	1.31 (1.02-1.67)	+++
Other	2	1.10 (0.95-1.28)	1.13 (0.89-1.45)	NS
Heterogeneity between continents				+
From mother specifically	9	0.96 (0.77-1.20)	0.98 (0.77-1.25)	NS
From father specifically	11	0.90 (0.80-1.00)	1.00 (0.78-1.29)	+++
From parents specifically	8	0.78 (0.64-0.94)	0.78 (0.64-0.94)	NS

[1]Significance levels indicated by +++$P < 0.001$, ++$P < 0.01$, +$P < 0.05$, (+) $P < 0.1$ for heterogeneity within level and for heterogeneity between level. NS: Not significant, $P \geqslant 0.1$.

were prospective (cohort) studies and 77 case-control. Twenty-two studies involved less than 50 cases in

Table 5 Estimates used when adjusting for potential confounding effects[1]

	Statistic	Fruit consumption	Vegetable consumption	Dietary fat consumption	Education
Lung cancer risk	N studies	14	16	6	12
	RR[2]	0.86	0.88	1.22	0.91
	(95%CI)	(0.78-0.96)[8]	(0.80-0.97)[8]	(1.09-1.36)[8]	(0.88-0.95)[6]
	per	SD	SD	SD	Year[3]
ETS exposure at home	N studies	11	16	12	13
	Difference[2,4]	-0.073[7]	-0.056[8]	0.131[7]	-0.534[6]
	(SE)	-0.02	-0.021	-0.032	-0.063
	unit	SD	SD	SD	Year[3]
Correlations[5]	Fruit consumption	1	+0.314[7]	-0.104[NS]	+0.143[NS]
	Vegetable consumption		1	-0.054[NS]	-0.130[9]
	Dietary fat consumption			1	-0.039[NS]
	Education				1

Note: *P* values are indicated by [6]$P < 0.001$, [7]$P < 0.01$, [8]$P < 0.05$, [9]$P < 0.1$, or [NS]$P \geqslant 0.1$. [1]All data are for lifelong non-smoking females; [2]Based on random-effects meta-analysis; [3]The SD for education was taken as 2.435 years based on six studies; [4]Difference in level of confounder between those exposed and unexposed to ETS at home; [5]Based on seven studies, using unweighted means.

Table 6 Adjusted/corrected analyses: Husband smoking[1]

Studies	*n*	Unadjusted for confounding Uncorrected for misclassification RR (95%CI)	Adjusted for confounding[2] Uncorrected for misclassification RR (95%CI)	Adjusted for confounding[2] Corrected for misclassification[3] RR (95%CI)
All	93	1.219 (1.138-1.305)	1.139 (1.062-1.221)	1.077 (0.999-1.162)
North America	29	1.074 (0.937-1.232)	1.004 (0.873-1.154)	0.898 (0.775-1.039)
Europe and New Zealand	20	1.174 (1.007-1.369)	1.092 (0.934-1.277)	1.062 (0.899-1.254)
China (including Hong Kong and study LIM)	27	1.321 (1.144-1.524)	1.239 (1.071-1.433)	1.175 (1.005-1.374)
Rest of Asia (including study ILCCO)	17	1.284 (1.187-1.389)	1.194 (1.103-1.291)	1.164 (1.072-1.262)
North America, Europe and New Zealand	49	1.112 (1.004-1.231)	1.037 (0.935-1.150)	0.959 (0.858-1.072)
Asia	44	1.314 (1.199-1.439)	1.229 (1.121-1.348)	1.181 (1.070-1.304)
Published in 1980s	26	1.361 (1.216-1.522)	1.267 (1.132-1.417)	1.194 (1.059-1.347)
Published in 1990s	27	1.152 (1.016-1.305)	1.077 (0.948-1.225)	1.005 (0.871-1.160)
Published in 2000s	26	1.240 (1.105-1.392)	1.163 (1.034-1.308)	1.115 (0.987-1.260)
Published in 2010s	14	1.139 (0.945-1.372)	1.059 (0.877-1.277)	1.026 (0.844-1.247)
< 100 cases	49	1.339 (1.178-1.521)	1.249 (1.098-1.422)	1.192 (1.038-1.370)
100-199 cases	22	1.117 (0.973-1.284)	1.042 (0.904-1.200)	0.978 (0.846-1.131)
200-399 cases	13	1.363 (1.190-1.561)	1.275 (1.114-1.460)	1.226 (1.051-1.429)
400+ cases	9	1.101 (0.973-1.247)	1.027 (0.905-1.166)	0.957 (0.826-1.108)
With dose-response data[4]	24	1.308 (1.181-1.449)	1.226 (1.105-1.359)	1.170 (1.052-1.302)
Without dose-response data	69	1.182 (1.088-1.286)	1.104 (1.014-1.201)	1.040 (0.948-1.141)
With age adjustment[5]	75	1.184 (1.100-1.274)	1.106 (1.027-1.191)	1.048 (0.966-1.136)
Without age adjustment	18	1.437 (1.194-1.728)	1.340 (1.110-1.618)	1.264 (1.026-1.556)
Case-control studies	77	1.226 (1.133-1.326)	1.144 (1.057-1.239)	1.080 (0.990-1.177)
Prospective studies	16	1.187 (1.043-1.350)	1.111 (0.977-1.264)	1.064 (0.928-1.220)

[1]All analyses use random-effects models; [2]Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education; [3]Using the Lee and Forey method[22] with an additive model and assuming a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia; [4]Specifically for smoking by the husband; [5]Or matching (within nonsmokers).

lifelong non-smokers, and nine over 400 cases.

Nine studies adjusted for fruit consumption, 11 for vegetables, and 4 for dietary fat. Less than half (32 studies) adjusted for an index of education.

Twenty-four of the studies provided data on lung cancer risk by amount smoked by the husband specifically, with the remainder only providing results for overall exposure. Table 1 of www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf gives the data used for each study and the fitted estimates of β and SEβ. Based on these data, it was estimated that each 10 cigarettes per day smoked by the husband multiplied risk by an estimated 1.09 (95%CI: 1.07-1.11) based on a fixed-effects analysis and 1.10 (1.07-1.14) using a random-effects analysis.

In order to adjust for the uncontrolled effects of confounding by diet (by fruit, vegetables and dietary fat) and education, summary estimates were required of the relationships of the four potential factors to both risk of lung cancer and ETS exposure, and of the correlations

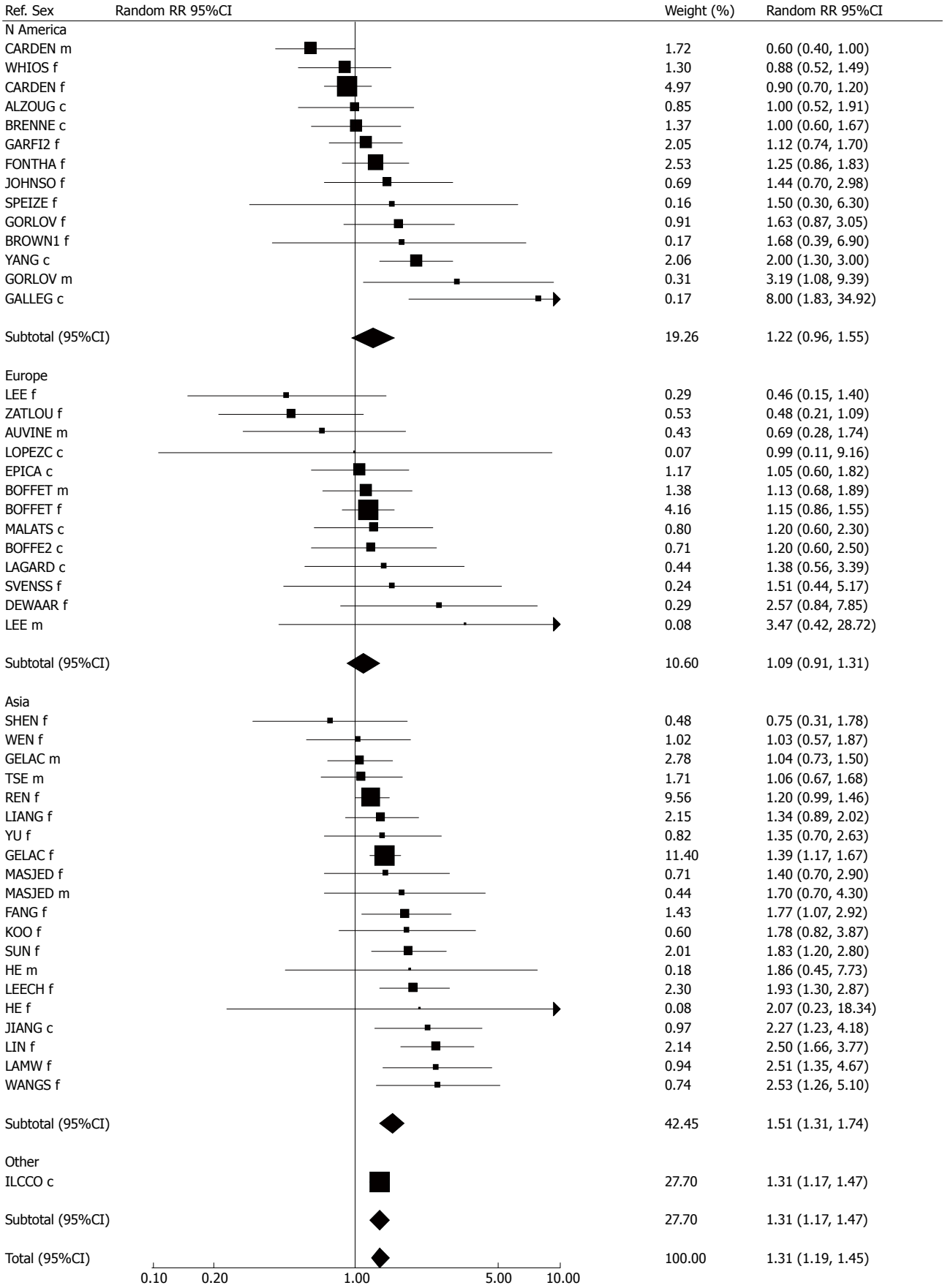


Figure 10 Forest plots for total environmental tobacco smoke exposure, by region. Estimates of the random-effects RR and its 95%CI are shown, separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%CIs and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

Table 7 Adjusted/corrected analyses: Per 10 cigs smoked by husband[1]

Studies	*n*	Unadjusted for confounding Uncorrected for misclassification RR (95%CI)	Adjusted for confounding[2] Uncorrected for misclassification RR (95%CI)	Adjusted for confounding[2] Corrected for misclassification[3] RR (95%CI)
All	93	1.102 (1.065-1.140)	1.062 (1.027-1.099)	1.032 (0.994-1.071)
North America	29	1.037 (0.977-1.101)	1.006 (0.946-1.070)	0.957 (0.896-1.022)
Europe and New Zealand	20	1.060 (0.995-1.128)	1.020 (0.956-1.088)	1.003 (0.938-1.073)
China (including Hong Kong and study LIM)	27	1.169 (1.082-1.263)	1.127 (1.041-1.219)	1.094 (1.006-1.191)
Rest of Asia (including study ILCCO)	17	1.142 (1.095-1.191)	1.094 (1.050-1.141)	1.079 (1.033-1.127)
North America, Europe and New Zealand	49	1.046 (1.001-1.094)	1.012 (0.967-1.059)	0.974 (0.928-1.023)
Asia	44	1.158 (1.104-1.216)	1.113 (1.060-1.170)	1.089 (1.033-1.147)
Published in 1980s	26	1.148 (1.092-1.207)	1.105 (1.052-1.162)	1.075 (1.019-1.134)
Published in 1990s	27	1.063 (1.004-1.125)	1.025 (0.967-1.087)	0.988 (0.926-1.053)
Published in 2000s	26	1.123 (1.056-1.194)	1.085 (1.020-1.155)	1.061 (0.995-1.132)
Published in 2010s	14	1.073 (0.970-1.188)	1.032 (0.932-1.143)	1.014 (0.912-1.128)
< 100 cases	49	1.143 (1.077-1.213)	1.101 (1.036-1.169)	1.072 (1.005-1.144)
100-199 cases	22	1.062 (0.993-1.137)	1.025 (0.957-1.098)	0.994 (0.926-1.066)
200-399 cases	13	1.176 (1.097-1.261)	1.134 (1.058-1.216)	1.111 (1.027-1.202)
400+ cases	9	1.041 (0.976-1.111)	1.002 (0.938-1.070)	0.966 (0.895-1.042)
With dose-response data[4]	24	1.123 (1.072-1.176)	1.082 (1.032-1.134)	1.053 (1.005-1.103)
Without dose-response data	69	1.091 (1.044-1.139)	1.053 (1.007-1.100)	1.021 (0.973-1.071)
With age adjustment[5]	75	1.084 (1.046-1.123)	1.044 (1.008-1.082)	1.015 (0.976-1.056)
Without age adjustment	18	1.211 (1.101-1.331)	1.168 (1.061-1.285)	1.131 (1.018-1.256)
Case-control studies	77	1.106 (1.064-1.150)	1.066 (1.025-1.109)	1.034 (0.991-1.080)
Prospective studies	16	1.081 (1.021-1.145)	1.043 (0.985-1.105)	1.018 (0.957-1.083)

[1]All analyses use random-effects models; [2]Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education; [3]Using the Lee and Forey method[22] with an additive model and assuming a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia; [4]Specifically for smoking by the husband; [5]Or matching (within nonsmokers).

between the four factors. The estimates used are presented in Table 5, and show that, in non-smoking females, both risk of lung cancer and ETS exposure at home are associated with reduced fruit and vegetable consumption and education, and increased dietary fat consumption. All these associations are significant at least at $P < 0.05$, and for education at $P < 0.001$, with the data based on analysis of results from at least 10 studies (with one exception - dietary fat and lung cancer, based on 6 studies). Table 5 also shows the inter-correlations between the four confounding variables, based on combined estimates from seven studies. These show that fruit and vegetable consumption are strongly correlated with each other ($P < 0.01$). Other correlations are weaker and not significant at $P < 0.05$.

As described in the methods, we used misclassification rates of 10% for Asian studies and 2.5% elsewhere, these rates accounting for the lower rates of lung cancer seen among misclassified smokers than among non-misclassified smokers.

Table 6 presents results of analyses adjusting for confounding and misclassification based on RRs for smoking by the husband, while Table 7 similarly presents results based on RRs per 10 cigarettes smoked by the husband. Each table presents three sets of results: (1) unadjusted; (2) adjusted for confounders; and (3) adjusted for confounders and corrected for smoking misclassification. They each give overall estimates and results subdivided by various aspects of the studies considered.

As shown in Table 6, adjustment for confounding variables reduces the overall RR for smoking by the husband from 1.219 (1.138 to 1.305) to 1.139 (1.062-1.221), implying bias due to failure to control for the four variables is 1.219/1.139 = 1.070. Further correction for misclassification reduced the estimate to a marginally nonsignificant 1.077 (0.999-1.162), implying a further bias of 1.139/1.077 = 1.058. In the fully adjusted and corrected analyses, there is no evidence of an association in North America, Europe and New Zealand (RR 0.959, 0.858-1.072) but there is an association in Asia (1.181, 1.070-1.304).

RRs are higher for studies providing dose-response data (1.170, 1.052-1.302) than for other studies (1.040, 0.948-1.141), and higher for studies which did not adjust for age (1.264, 1.026-1.556) than for those which did (1.048, 0.966-1.136). However, neither difference is statistically significant ($P = 0.10$ and $P = 0.08$ respectively).

The pattern of results shown in Table 7, where RRs are per amount smoked by the husband, is similar, though the RRs themselves are lower. Thus, the unadjusted/uncorrected overall RR of 1.102 (1.065-1.140) reduces to 1.062 (1.027-1.099) after adjustment for confounding (bias = 1.038), and to a nonsignificant 1.032 (0.994-1.071) after further correction for misclassification (additional bias = 1.030). Patterns of variation by study factors are very similar to those for overall smoking by the husband in Table 6.

Additional material presented in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf shows that the effect of confounder adjustment was greatest for education, and least for fruit and vegetables. Thus, in the analysis of RRs per amount smoked by the husband, the

biases due to uncontrolled confounding were estimated as 1.024 for education, 1.013 for dietary fat, 1.005 for fruit, and 1.004 for vegetables.

DISCUSSION

Introduction

We have demonstrated, as other reviews before us[6,76], a weak but significant ($P < 0.05$) association of ETS exposure with never smoker lung cancer risk. This can be seen for various indices of exposure, including spousal, household, workplace and total exposure. It is less clearly evident for exposure in travel and in social situations, where data are quite limited, and for childhood exposure where the results shown in Table 4 are rather conflicting. There is also clear heterogeneity between study-specific estimates for many of the indices of exposure. Meta-analyses for smoking by the spouse (or nearest equivalent) shown in Table 3 indicate that estimates are higher in early studies (published in 1981-89), in small studies (1-49 cases), and where estimates are not age-adjusted.

Do these quite weak associations provide good evidence of a causal relationship? To gain insight into this we carried out additional analyses for smoking by the husband investigating biases due to uncontrolled confounding by education and three aspects of diet (fruit, vegetables and dietary fat) and due to failure to adjust for misclassification of smoking by the subject. Based on 93 studies, confounder adjustment and misclassification correction substantially reduced the magnitude of the association with smoking by the husband, the RR (95%CI) estimate of 1.22 (1.14-1.31) reducing to 1.14 (1.06-1.22) after confounder adjustment, and further reducing to 1.08 (0.999-1.16) after additional correction for misclassification. The adjusted and corrected estimate is not quite significant, the same being true for analyses based on the RR per 10 cigs/day smoked by the spouse, where the overall RR reduced from 1.10 (1.07-1.14) to 1.06 (1.03-1.10) after adjustment for confounding and to 1.03 (0.994-1.07) after the further correction for misclassification.

Below we discuss some aspects of the evidence relevant to consideration of causality. Parts of the discussion are quite brief, the interested reader being referred to our publication[2] describing our earlier analyses.

Plausibility

Since active smoking causes lung cancer, and since ETS contains many of the carcinogens in tobacco smoke, it can be argued that some causal effect of ETS exposure is to be expected, though this argument depends on there being no threshold dose of exposure. If there is no threshold, what effect might one expect? Certainly, exposure from ETS is much less than that from active smoking, with studies based on cotinine indicating relative exposure factors of 0.4%[77], 0.2%[78] or 0.06%[79] and studies based on particulate matter[80-88] suggesting a lower factor, of order 0.005%-0.02%. Given an RR for current *vs* never smoking of 8.43, as reported in a recent meta-analysis[89] and assuming a linear dose-response relationship, even a relative exposure factor as high as 0.5% would only suggest that the RR for ETS exposure would be about 1.04, while a relative exposure factor of 0.1% would suggest a RR of about 1.008. These RRs are much less than the unadjusted/uncorrected RR of 1.22 for smoking by the husband (or nearest equivalent) shown in Table 6. Either the relationship between dose and risk is distinctly non-linear (and the evidence does not suggest this for active smoking[89]) or a substantial part, if not all, of the observed association is due to bias.

Confounding

Based on the evidence we collected, we have demonstrated a clear tendency for increased dietary fat consumption, reduced fruit and vegetable consumption and fewer years of education to be associated both with increased lung cancer risk and with increased at home ETS exposure. Given that relatively few of the studies adjusted for the dietary variables or education, it was to be expected that adjustment for these four factors would reduce the RR for smoking by the husband, and so it proved. While there is uncertainty in this adjustment, as discussed elsewhere[19], it is clear that there is a considerable potential for bias. Among other things it should be noted that these are not the only potential sources of bias. We considered various other candidate confounding factors, including income, occupation, and socioeconomic factors, obesity, physical activity, air pollution, alcohol and tea drinking, but concluded that for none of these were there data adequate to provide any sort of reliable qualitative estimate of their relationship to lung cancer risk in non-smokers. That said, the general tendency for smoking and marriage to a smoker to be associated with lifestyle factors generally considered associated with adverse health[90-93], suggests that our adjustments may well have been conservative.

Misclassification of active smoking

Some current or former smokers are known to deny having smoked, so being wrongly described as never smokers[26,94]. Also, marital partners' smoking habits are correlated, with smokers tending to marry smokers[3,23]. Taken together, these two tendencies, if ignored, will bias the observed association of smoking by the husband to never smoker lung cancer risk[3,21,95]. There are many difficulties in accurately estimating the extent of bias due to misclassification. These include the misclassification rates being dependent on the circumstances in which the questions were asked, as well as the fact that smokers who deny smoking are unrepresentative of all smokers, tending to be more often occasional smokers and long-term ex-smokers and so have lower lung cancer risks than non-misclassified smokers[23]. Here we have assumed, as earlier[22], that misclassification correction can be carried out assuming that, among women, the percentage of average-risk ever-smokers who deny smoking is 10.0% in Asia and 2.5% elsewhere, these

misclassification rates taking account of the lower lung cancer rates in misclassified compared to non-misclassified smokers.

While the misclassification correction is clearly open to question, and we have not formally updated the extensive work we did some years ago on estimating rates[23,26], we still believe that the rates we have used are not unreasonable. Indeed given recent estimates of substantial denial of smoking in recent studies[94,96,97], our correction may be somewhat conservative.

We now briefly comment on other sources of bias.

Publication bias

Publication bias occurs if the data that are published are not representative of all the data that exist on a topic. For many exposures, positive findings are published more often than negative findings[98-100], so meta-analyses of data drawn from the literature overestimate true relationships. We have not attempted to quantify the extent of publication bias, though our detailed tables (www.pnlee.co.uk/downloads/etslc/23482-supplementary file 4.pdf) do include results of Egger tests[16], a number showing some evidence that smaller studies are more likely to produce above average than below average RRs. This is consistent with the higher RRs reported in small studies seen in Table 3 for spousal smoking. We believe that some publication bias exists but given that the larger studies seem likely to publish regardless of the findings, and that these contribute most to the overall estimates, such bias is probably unimportant.

There is some evidence (P = 0.10) that RRs are higher for those studies which provide dose-response results than for those which do not so. If this represents a true effect, it is suggestive of a different form of publication bias, with authors tending to be more likely to report dose-response results where there is a strong association in the first place.

Diagnostic inaccuracy

Misdiagnosis of lung cancer certainly exists, especially when based on X-rays or sputum cytology[101-103]. The extent, and direction, to which it might have biased the RR estimate for ETS and lung cancer is difficult to determine. While randomly misdiagnosing as lung cancer diseases which are unassociated with ETS would tend to dilute any true RR, misdiagnosis might not be random and may be correlated with ETS exposure or factors associated with it. Since random-effects estimates for spousal smoking proved to be quite similar for studies that did or did not require full histological confirmation, this seems unlikely to be an important source of bias.

Errors in determining ETS exposure

Case-control studies collect exposure data after the disease has occurred, and the presence of the disease itself, or knowledge of it, may distort responses about past exposure. Such recall bias is not an issue for prospective studies. Given that our analyses for spousal smoking found little difference in RRs by study type, we feel that recall bias is unlikely to be a major problem.

Random misclassification of smoking spouses as non-smokers will not create a false effect if no true risk exists, but will underestimate a true relationship. It has been clearly shown[21] that such misclassification causes much less bias effect than does misclassification of the subject's smoking, so for practical purposes it can be ignored.

Bias from ETS exposure in the reference group

When considering the relationship of lung cancer risk to smoking by the husband, three categories of women are relevant: A - never smokers married to ever smokers; B - never smokers married to never smokers; and C - never smokers without any ETS exposure. Group C is a subset of group B. In the analysis of the effect of husband's smoking, the RR estimate is based on comparison of groups A and B, but it has been argued[3] that a better estimate RR* is based on comparison of groups A and C. If a marker of ETS exposure, such as cotinine, is Z times higher in group A than group B, RR* can be estimated by RR* = RR(Z-1) / (Z-RR)[2,3].

Some comments can be made on this revised estimate. First, and most noteworthy, to conduct background correction only makes sense when the original association, with marriage to a smoker, derives from a causal effect of ETS. Where adjustment for confounding and correction for smoker misclassification bias explains the whole of the observed association, background correction will have no effect. If such adjustment and correction explains most of the association, the correction will have a small effect. Thus, assuming Z = 3, as estimated by Hackshaw *et al*[3], this correction has quite a substantial effect on the unadjusted association for husband's smoking, increasing it from 1.22 to 1.37. However, applying it to the confounder adjusted and misclassification corrected estimate of 1.08 only increases it to 1.12. In any case, the validity of the background-corrected estimate of 1.12 is dubious, given that the 1.08 was not statistically significant in the first place, and could itself be an overestimate due to the limitations in confounder adjustment and misclassification correction discussed above.

Second, background correction only applies to the simple comparison of risk in the exposed and comparison groups, and does not apply to estimates of the increase in risk for amount smoked by the husband. Also, background correction is only an indirect method for estimating lung cancer risk from sources of ETS exposure other than the spouse, using data only relating to spousal exposure. This method ignores existing data on risk from these other sources.

Overall impression

Coming to reliable conclusions regarding a weak association based on non-randomized epidemiological studies is difficult at the best of times. When, as here, there is evidence that adjustment for confounding and correction for misclassification substantially weakens the association most usually considered (smoking by

the husband) and renders it nonsignificant, and when these adjustments and corrections may themselves be somewhat limited, one cannot reliably conclude that a true effect of ETS exposure on lung cancer risk has been demonstrated. While one cannot prove a negative, and while the clear relationship of smoking to lung cancer suggests that some association might exist, the only conclusion that seems valid is that there may be a relationship of ETS to lung cancer risk (with the evidence stronger for Asian studies), but if it exists, it is certainly much weaker than suggested by meta-analyses that do not adjust for confounding and misclassification.

Most, if not all, of the weak association of ETS with risk of lung cancer is explicable by confounding and smoking misclassification. A causal relationship is not demonstrated.

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COMMENTS

Background

The authors address the widely held claim that environmental tobacco smoke (ETS) exposure causes lung cancer by presenting an up-to-date comprehensive meta-analysis of the available evidence, considering exposure from various sources, and illustrating the potential magnitude of bias from confounding and misclassification of smoking.

Research frontiers

Based on all 102 studies providing relevant data, the authors demonstrate a significant ($P < 0.05$) increase in never smoker lung cancer risk for various exposure indices - from the spouse, at home, at work and overall, though the evidence for childhood exposure is less clear. Based on smoking by the husband, the most studied ETS exposure index, the RR is estimated as 1.22 (95%CI: 1.14-1.31). However, adjustment for confounding by education and by consumption of fruit, vegetables and dietary fat, and correction for misclassification of active smoking by the wife, markedly reduces this association, which becomes a nonsignificant 1.08 (95%CI: 0.999-1.16). Since these adjustments and corrections may not fully correct for the bias from these sources, and given the existence of other biases, one cannot conclude with any certainty that a true effect of ETS exposure on lung cancer risk exists.

Innovations and breakthroughs

The new feature of the paper is the extent of the evidence considered, and the adjustments and corrections made.

Applications

The authors analysis should engender caution in drawing inferences from weak associations seen in non-randomized epidemiological studies, particularly where biases are known to exist.

Peer-review

It is an interesting paper.

REFERENCES

1 **International Agency for Research on Cancer**. Tobacco smoke and involuntary smoking. IARC Monographs on the evaluation of carcinogenic risks to humans Lyon, France: IARC, 2004. Available from: URL: http//monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf

2 **Lee PN**, Fry JS, Forey BA. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. *Indoor Built Environ* 2002; **11**: 59-82 [DOI: 10.1177/1420326X0201100202]

3 **Hackshaw AK**, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997; **315**: 980-988 [PMID: 9365295 DOI: 10.1136/bmj.315.7114.980]

4 **Zhong L**, Goldberg MS, Parent ME, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer* 2000; **27**: 3-18 [PMID: 10672779 DOI: 10.1016/S0169-5002(99)00093-8]

5 **Taylor R**, Cumming R, Woodward A, Black M. Passive smoking and lung cancer: a cumulative meta-analysis. *Aust N Z J Public Health* 2001; **25**: 203-211 [PMID: 11494987 DOI: 10.1111/j.1467-842X.2001.tb00564.x]

6 **Boffetta P**. Involuntary smoking and lung cancer. *Scand J Work Environ Health* 2002; **28** Suppl 2: 30-40 [PMID: 12058801]

7 **Stayner L**, Bena J, Sasco AJ, Smith R, Steenland K, Kreuzer M, Straif K. Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health* 2007; **97**: 545-551 [PMID: 17267733 DOI: 10.2105/AJPH.2004.061275]

8 **Taylor R**, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol* 2007; **36**: 1048-1059 [PMID: 17690135 DOI: 10.1093/ije/dym]

9 **Zhao H**, Gu J, Xu H, Yang B, Han Y, Li L, Liu S, Yao H. [Meta-analysis of the relationship between passive smoking population in China and lung cancer]. *Zhongguo Fei Ai Za Zhi* 2010; **13**: 617-623 [PMID: 20681450 DOI: 10.3779/j.issn.1009-3419.2010.06.010]

10 **Wang X**, Qin Y, Gu J, Wang F, Jia P, Wang H, Yao Q, Zhu S. [Systematic review of studies of workplace exposure to environmental tobacco smoke and lung cancer risk]. *Zhongguo Fei Ai Za Zhi* 2011; **14**: 345-350 [PMID: 21496434 DOI: 10.3779/j.issn.1009-3419.2011.04.08]

11 **Lee PN**. An assessment of the epidemiological evidence relating lung cancer risk in never smokers to environmental tobacco smoke exposure. In: Kasuga H. Environmental tobacco smoke, Discussion on ETS, Tokyo. New York: Springer-Verlag, 1993: 28-70

12 **Gardner MJ**, Altman DG, editors. Statistics with confidence. Confidence intervals and statistical guidelines. London: British Medical Journal, 1989

13 **Fleiss JL**, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol* 1991; **44**: 127-139 [PMID: 1995774 DOI: 10.1016/0895-4356(91)90261-7]

14 **Hamling J**, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008; **27**: 954-970 [PMID: 17676579 DOI: 10.1002/sim.3013]

15 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

16 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]

17 **Fry JS**, Lee PN. Revisiting the association between environmental

tobacco smoke exposure and lung cancer risk. I. The dose-response relationship with amount and duration of smoking by the husband. *Indoor Built Environ* 2000; **9**: 303-316 [DOI: 10.1177/1420326X00 00900602]

18 **Greenland S**, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; **135**: 1301-1309 [PMID: 1626547]

19 **Fry JS**, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. II. Adjustment for the potential confounding effects of fruit, vegetables, dietary fat and education. *Indoor Built Environ* 2001; **10**: 20-39 [DOI: 10.1177/142 0326X0101000103]

20 **Lee** PN, Fry JS. The relationship between lung cancer and ETS exposure: adjustment for the potential confounding effects of multiple risk factors and for misclassification of active smoking status. Updated analyses. Sutton, Surrey: P N Lee Statistics and Computing Ltd, 2006. Available from: URL: http//www.pnlee.co.uk/Reports.htm

21 **Lee PN**, Forey BA. Misclassification of smoking habits as a source of bias in the study of environmental tobacco smoke and lung cancer. *Stat Med* 1996; **15**: 581-605 [PMID: 8731002 DOI: 10.1002 /(SICI)1097-0258(19960330)15]

22 **Lee PN**, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. III. Adjustment for the biasing effect of misclassification of smoking habits. *Indoor Built Environ* 2001; **10**: 384-398 [DOI: 10.1177/1420 326X0101000605]

23 **Lee PN**. Environmental tobacco smoke and mortality. A detailed review of epidemiological evidence relating environmental tobacco smoke to the risk of cancer, heart disease and other causes of death in adults who have never smoked. Basel: Karger, 1992

24 **National Cancer Institute**. Shopland DR, editor. Respiratory health effects of passive smoking: lung cancer and other disorders. The report of the US Environmental Protection Agency. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1993. Available from: URL: http//cancercontrol.cancer.gov/tcrb/monographs/

25 **Lee P**. Passive smoking and lung cancer. Strength of evidence on passive smoking and lung cancer is overstated. *BMJ* 1998; **317**: 346-347; author reply 348 [PMID: 9685291 DOI: 10.1136/ bmj.317.7154.346]

26 **Lee PN**, Forey BA. Misclassification of smoking habits as determined by cotinine or by repeated self-report - a summary of evidence from 42 studies. *J Smoking-Related Dis* 1995; **6**: 109-129

27 **Trichopoulos D**, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of Greek study. *Lancet* 1983; **2**: 677-678 [PMID: 6136810 DOI: 10.1016/S0140-6736(83)92549-7]

28 **Hirayama T**. Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P, editors. Lung cancer: causes and prevention, Proceedings of the International Lung Cancer Update Conference, New Orleans, Louisiana, March 3-5, 1983. Deerfield Beach, Florida: Verlag Chemie International, Inc, 1984: 175-195

29 **Lam WK**. A clinical and epidemiological study of carcinoma of lung in Hong Kong [Thesis]. University of Hong Kong, 1985. Available from: URL: http//hub.hku.hk/handle/10722/28030

30 **Lam TH**, Kung IT, Wong CM, Lam WK, Kleevens JW, Saw D, Hsu C, Seneviratne S, Lam SY, Lo KK. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. *Br J Cancer* 1987; **56**: 673-678 [PMID: 3426935 DOI: 10.1038/bjc.1987.264]

31 **Geng GY**, Liang ZH, Zhang AY, Wu GL. On the relationship between cigarette smoking and female lung cancer. In: Aoki M, Hisamichi S, Tominaga S, editors. Smoking and health 1987, Proceedings of the 6th World Conference on Smoking and Health, Tokyo, 9-12 November 1987. Amsterdam: Elsevier Science Publishers B.V. (Biomedical Division), 1988: 483-486 International Congress Series No. 780

32 **Kalandidi A**, Katsouyanni K, Voropoulou N, Bastas G, Saracci R, Trichopoulos D. Passive smoking and diet in the etiology of lung cancer among non-smokers. *Cancer Causes Control* 1990; **1**: 15-21 [PMID: 1966316 DOI: 10.1007/BF00053179]

33 **Fontham ET**, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, Chen VW, Alterman T, Boyd P, Austin DF. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA* 1994; **271**: 1752-1759 [PMID: 8196118 DOI: 10.1001/jama.1994.03510460044031]

34 **Wang SY**, Hu YL, Wu YL, Li X, Chi GB, Chen Y, Dai WS. A comparative study of the risk factors for lung cancer in Guangdong, China. *Lung Cancer* 1996; **14** Suppl 1: S99-105 [PMID: 8785673 DOI: 10.1016/S0169-5002(96)90215-9]

35 **Zheng S**, Fan R, Wu Z. [Studies on relationship between passive smoking and lung cancer in non-smoking women]. *Zhonghua Yu Fang Yi Xue Za Zhi* 1997; **31**: 163-165 [PMID: 9812596]

36 **Zaridze D**, Maximovitch D, Zemlyanaya G, Aitakov ZN, Boffetta P. Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. *Int J Cancer* 1998; **75**: 335-338 [PMID: 9455789 DOI: 10.1002/(SICI)1097-0215(199 80130)75]

37 **Lee CH**, Ko YC, Goggins W, Huang JJ, Huang MS, Kao EL, Wang HZ. Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. *Int J Epidemiol* 2000; **29**: 224-231 [PMID: 10817117 DOI: 10.1093/ ije/29.2.224]

38 **Fang J**, Gan DK, Zheng SH, Zhang HW. [A case-control study of the risk factors for lung cancer among Chinese women who have never smoked]. *Wei Sheng Yan Jiu* 2006; **35**: 464-467 [PMID: 16986525]

39 **Yang P**, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, Wampfler JA, Thibodeau SN, Katzmann JA, Allen MS, Midthun DE, Marks RS, de Andrade M. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. *Arch Intern Med* 2008; **168**: 1097-1103 [PMID: 18504338 DOI: 10.1001/archinte.168.10.1097]

40 **Liang H**, Guan P, Yin Z, Li X, He Q, Zhou B. Risk of lung cancer following nonmalignant respiratory conditions among nonsmoking women living in Shenyang, Northeast China. *J Womens Health* (Larchmt) 2009; **18**: 1989-1995 [PMID: 20044861 DOI: 10.1089/ jwh.2008.1355]

41 **Jiang T**, Song H, Peng X, Yan L, Yu M, Liu Y, Liu H, Liu F, Lu Y. [A case-control study on non-smoking primary lung cancers in Sichuan, China]. *Zhongguo Fei Ai Za Zhi* 2010; **13**: 511-516 [PMID: 20677651 DOI: 10.3779/j.issn.1009-3419.2010.05.24]

42 **Lin Y**, Cai L. Environmental and dietary factors and lung cancer risk among Chinese women: a case-control study in southeast China. *Nutr Cancer* 2012; **64**: 508-514 [PMID: 22489989 DOI: 10.1080/01635581.2012.668743]

43 **Lo YL**, Hsiao CF, Chang GC, Tsai YH, Huang MS, Su WC, Chen YM, Hsin CW, Chang CH, Yang PC, Chen CJ, Hsiung CA. Risk factors for primary lung cancer among never smokers by gender in a matched case-control study. *Cancer Causes Control* 2013; **24**: 567-576 [PMID: 22729933 DOI: 10.1007/s10552-012-9994-x]

44 **Masjedi MR**, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, Karimi S, Hosseini M, Mortaz E. Opium could be considered an independent risk factor for lung cancer: a case-control study. *Respiration* 2013; **85**: 112-118 [PMID: 22759984 DOI: 10.1159/000338559]

45 **Kim CH**, Lee YC, Hung RJ, McNallan SR, Cote ML, Lim WY, Chang SC, Kim JH, Ugolini D, Chen Y, Liloglou T, Andrew AS, Onega T, Duell EJ, Field JK, Lazarus P, Le Marchand L, Neri M, Vineis P, Kiyohara C, Hong YC, Morgenstern H, Matsuo K, Tajima K, Christiani DC, McLaughlin JR, Bencko V, Holcatova I, Boffetta P, Brennan P, Fabianova E, Foretova L, Janout V, Lissowska J, Mates D, Rudnai P, Szeszenia-Dabrowska N, Mukeria A, Zaridze D, Seow A, Schwartz AG, Yang P, Zhang ZF. Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). *Int J Cancer* 2014; **135**: 1918-1930 [PMID: 24615328 DOI: 10.1002/ ijc.28835]

46 **Wu-Williams AH**, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, Stone BJ, Yu SF, Feng YP, Ershow AG. Lung cancer among women in north-east China. *Br J Cancer* 1990; **62**: 982-987 [PMID: 2257230 DOI: 10.1038/bjc.1990.421]

47 **Brenner DR**, Hung RJ, Tsao MS, Shepherd FA, Johnston MR, Narod S, Rubenstein W, McLaughlin JR. Lung cancer risk in never-smokers: a population-based case-control study of epidemiologic risk factors. *BMC Cancer* 2010; **10**: 285 [PMID: 20546590 DOI: 10.1186/1471-2407-10-285]

48 **Al-Zoughool M**, Pintos J, Richardson L, Parent MÉ, Ghadirian P, Krewski D, Siemiatycki J. Exposure to environmental tobacco smoke (ETS) and risk of lung cancer in Montreal: a case-control study. *Environ Health* 2013; **12**: 112 [PMID: 24345091 DOI: 10.1186/1476-069X-12-112]

49 **Neuberger JS**, Mahnken JD, Mayo MS, Field RW. Risk factors for lung cancer in Iowa women: implications for prevention. *Cancer Detect Prev* 2006; **30**: 158-167 [PMID: 16581199 DOI: 10.1016/j.cdp.2006.03.001]

50 **Pandey A**, Sharma S. Abstracts of the ISEE (International Society of Environmental Epidemiology) 20th Annual Conference. Pasadena, California, USA. October 12-16, 2008. *Epidemiology* 2008; **19** Suppl 6: S13-379 [PMID: 18854715 DOI: 10.1097/01.ede.0000340438.65758.2f]

51 **Gallegos-Arreola MP**, Figuera-Villanueva LE, Troyo-Sanroman R, Morgán-Villela G, Puebla-Pérez AM, Flores-Marquez MR, Zúniga-González GM. CYP1A1 *2B and *4 polymorphisms are associated with lung cancer susceptibility in Mexican patients. *Int J Biol Markers* 2008; **23**: 24-30 [PMID: 18409147]

52 **Du YX**, Cha Q, Chen YZ, Wu JM. Exposure to environmental tobacco smoke and female lung cancer in Guangzhou, China. In: Proceedings of Indoor. 1993: 511-516

53 **Kabat GC**, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984; **53**: 1214-1221 [PMID: 6692309 DOI: 10.1002/1097-0142(19840301)53]

54 **Zhong L**, Goldberg MS, Gao YT, Jin F. A case-control study of lung cancer and environmental tobacco smoke among nonsmoking women living in Shanghai, China. *Cancer Causes Control* 1999; **10**: 607-616 [PMID: 10616829]

55 **Gorlova OY**, Zhang Y, Schabath MB, Lei L, Zhang Q, Amos CI, Spitz MR. Never smokers and lung cancer risk: a case-control study of epidemiological factors. *Int J Cancer* 2006; **118**: 1798-1804 [PMID: 16217766 DOI: 10.1002/ijc.21561]

56 **Wen W**, Shu XO, Gao YT, Yang G, Li Q, Li H, Zheng W. Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. *BMJ* 2006; **333**: 376 [PMID: 16837487 DOI: 10.1136/bmj.38834.522894.2F]

57 **Schwartz AG**, Yang P, Swanson GM. Familial risk of lung cancer among nonsmokers and their relatives. *Am J Epidemiol* 1996; **144**: 554-562 [PMID: 8797515]

58 **Stockwell HG**, Goldman AL, Lyman GH, Noss CI, Armstrong AW, Pinkham PA, Candelora EC, Brusa MR. Environmental tobacco smoke and lung cancer risk in nonsmoking women. *J Natl Cancer Inst* 1992; **84**: 1417-1422 [PMID: 1512793 DOI: 10.1093/jnci/84.18.1417]

59 **Zeka A**, Mannetje A, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabiánová E, Mates D, Bencko V, Navratilova M, Cassidy A, Janout V, Travier N, Fevotte J, Fletcher T, Brennan P, Boffetta P. Lung cancer and occupation in nonsmokers: a multicenter case-control study in Europe. *Epidemiology* 2006; **17**: 615-623 [PMID: 17068414 DOI: 10.1097/01.ede.0000239582.92495.b5]

60 **Sun XW**, Dai XD, Lin CY, Shi YB, Ma YY, Li W. Environmental tobacco smoke (ETS) and lung cancer among nonsmoking women in Harbin. *Lung Cancer* 1996; **14** (Suppl 1): S237

61 **Rapiti E**, Jindal SK, Gupta D, Boffetta P. Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer* 1999; **23**: 183-189 [PMID: 10413195 DOI: 10.1016/S0169-5002(99)00013-6]

62 **Wang L**, Lubin JH, Zhang SR, Metayer C, Xia Y, Brenner A, Shang B, Wang Z, Kleinerman RA. Lung cancer and environmental tobacco smoke in a non-industrial area of China. *Int J Cancer* 2000; **88**: 139-145 [PMID: 10962452 DOI: 10.1002/1097-0215(20001001)88]

63 **Rachtan J**. Smoking, passive smoking and lung cancer cell types among women in Poland. *Lung Cancer* 2002; **35**: 129-136 [PMID: 11804684 DOI: 10.1016/S0169-5002(01)00330-0]

64 **Zatloukal P**, Kubík A, Pauk N, Tomásek L, Petruzelka L. Adenocarcinoma of the lung among women: risk associated with smoking, prior lung disease, diet and menstrual and pregnancy history. *Lung Cancer* 2003; **41**: 283-293 [PMID: 12928119 DOI: 10.1016/S0169-5002(03)00234-4]

65 **Olivo-Marston SE**, Yang P, Mechanic LE, Bowman ED, Pine SR, Loffredo CA, Alberg AJ, Caporaso N, Shields PG, Chanock S, Wu Y, Jiang R, Cunningham J, Jen J, Harris CC. Childhood exposure to secondhand smoke and functional mannose binding lectin polymorphisms are associated with increased lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 3375-3383 [PMID: 19959685 DOI: 10.1158/1055-9965.EPI-09-0986]

66 **Boffetta P**, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jöckel KH, Krauss M, Kreienbrock L, Kreuzer M, Mendes A, Merletti F, Nyberg F, Pershagen G, Pohlabeln H, Riboli E, Schmid G, Simonato L, Trédaniel J, Whitley E, Wichmann HE, Winck C, Zambon P, Saracci R. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *J Natl Cancer Inst* 1998; **90**: 1440-1450 [PMID: 9776409 DOI: 10.1093/jnci/90.19.1440]

67 **Correa P**, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. *Lancet* 1983; **2**: 595-597 [PMID: 6136747 DOI: 10.1016/S0140-6736(83)90680-3]

68 **Akiba S**, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. *Cancer Res* 1986; **46**: 4804-4807 [PMID: 3731126]

69 **Lee YA**, Hung R, Boffetta P, Brennan P, Christiani D, Duell EJ, Field JK, Kiyohara C, Lan Q, Lazarus P, Le Marchand L, Matsuo K, McLaughlin JR, Neri M, Schwartz A, Seow A, Tajima K, Vineis P, Yang P, Zhang ZF. A pooled analysis on the associations between involuntary smoking and lung cancer risk by histological types [Abstract]. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 892-893 [DOI: 10.1158/1055-9965.EPI-19-3-ASPO05]

70 **Shimizu H**, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M, Nishimura M, Kunishima K, Karasawa K, Nishiwaki K. A case-control study of lung cancer in nonsmoking women. *Tohoku J Exp Med* 1988; **154**: 389-397 [PMID: 3188004 DOI: 10.1620/tjem.154.389]

71 **Franco-Marina F**, Villalba Caloca J, Corcho-Berdugo A. Role of active and passive smoking on lung cancer etiology in Mexico City. *Salud Publica Mex* 2006; **48** Suppl 1: S75-S82 [PMID: 17684692 DOI: 10.1590/S0036-36342006000700009]

72 **Janerich DT**, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, Zaman MB, Melamed MR, Kiely M, McKneally MF. Lung cancer and exposure to tobacco smoke in the household. *N Engl J Med* 1990; **323**: 632-636 [PMID: 2385268 DOI: 10.1056/NEJM199009063231003]

73 **Cardenas VM**, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, Heath CW. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study. II. *Cancer Causes Control* 1997; **8**: 57-64 [PMID: 9051323 DOI: 10.1023/A: 1018483121625]

74 **Lim WY**, Chen Y, Chuah KL, Eng P, Leong SS, Lim E, Lim TK, Ng A, Poh WT, Tee A, Teh M, Salim A, Seow A. Female reproductive factors, gene polymorphisms in the estrogen metabolism pathway, and risk of lung cancer in Chinese women. *Am J Epidemiol* 2012; **175**: 492-503 [PMID: 22331461 DOI: 10.1093/aje/kwr332]

75 **Garfinkel L**. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J Natl Cancer Inst* 1981; **66**: 1061-1066 [PMID: 6941041 DOI: 10.1093/jnci/66.6.1061]

76 **International Agency for Research on Cancer**. Second-hand tobacco smoke. In: A review of human carcinogens: Part E: Personal habits and indoor combustions. Volume 100. Lyon, France: IARC, 2012: 215-265

77 **Office of Population Censuses and Surveys**. Colhoun H, Prescott-Clarke P, editors. Health survey for England 1994. Volume I: Findings. Volume II: Survey methodology & documentation. London: HMSO, 1996

78 **Ziegler RG**, Mason TJ, Stemhagen A, Hoover R, Schoenberg JB, Gridley G, Virgo PW, Altman R, Fraumeni JF, Jr. Dietary carotene and vitamin A and risk of lung cancer among white men in New Jersey. *J Natl Cancer Inst* 1984; **73**: 1429-1435 [PMID: 6595451

DOI: 10.1093/jnci/73.6.1429]
79 **Pirkle JL**, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *JAMA* 1996; **275**: 1233-1240 [PMID: 8601954 DOI: 10.1001/jama.275.16.1233]
80 **Benowitz NL**, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. *Am J Epidemiol* 2009; **169**: 236-248 [PMID: 19019851 DOI: 10.1093/aje/kwn301]
81 **Phillips K**, Bentley MC, Howard DA, Alván G. Assessment of air quality in Stockholm by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Scand J Work Environ Health* 1996; **22** Suppl 1: 1-24 [PMID: 8817762 DOI: 10.1016/0160-4120(94)90303-4]
82 **Phillips K**, Bentley MC, Howard DA, Alván G, Huici A. Assessment of air quality in Barcelona by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. *Environ Int* 1997; **23**: 173-196 [DOI: 10.1016/S0160-4120(97)00004-4]
83 **Phillips K**, Howard DA, Bentley MC, Alván G. Assessment of air quality in Kuala Lumpur by personal monitoring of nonsmokers at home and in the workplace by reference to respirable suspended particles (RSP) and environmental tobacco smoker (ETS). In: Gee IL, Leslie GB, editors. Indoor and built environment problems in Asia, Proceedings of a conference held in Kuala Lumpur, Malaysia on 4th & 5th September 1997. Rothenfluh, Switzerland: The International Society of the Built Environment, 1997: 151-159
84 **Phillips K**, Howard DA, Bentley MC, Alván G. Assessment by personal monitoring of respirable suspended particles and environmental tobacco smoke exposure for non-smokers in Sydney, Australia. *Indoor Built Environ* 1998; **7**: 188-203 [DOI: 10.1177/1420326X9800700403]
85 **Phillips K**, Howard DA, Bentley MC. Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Lisbon by personal monitoring. *Environ Int* 1998; **24**: 301-324 [DOI: 10.1016/S0160-4120(98)00009-9]
86 **Phillips K**, Howard DA, Bentley MC, Alván G. Measured exposures by personal monitoring for respirable suspended particles and environmental tobacco smoke of housewives and office workers resident in Bremen, Germany. *Int Arch Occup Environ Health* 1998; **71**: 201-212 [PMID: 9591162 DOI: 10.1007/s004200050271]
87 **Phillips K**, Bentley MC, Howard DA, Alván G. Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Prague using personal monitoring. *Int Arch Occup Environ Health* 1998; **71**: 379-390 [PMID: 9766911 DOI: 10.1007/s004200050296]
88 **Phillips K**, Howard DA, Bentley MC, Alván G. Environmental tobacco smoke and respirable suspended particle exposures for non-smokers in Beijing. *Indoor Built Environ* 1998; **7**: 254-269 [DOI: 10.1177/1420326X9800700503]
89 **Lee PN**, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer* 2012; **12**: 385 [PMID: 22943444 DOI: 10.1186/1471-2407-12-385]
90 **Thornton A**, Lee P, Fry J. Differences between smokers, ex-smokers, passive smokers and non-smokers. *J Clin Epidemiol* 1994; **47**: 1143-1162 [PMID: 7722548 DOI: 10.1016/0895-4356(94)90101-5]
91 **Dallongeville J**, Marécaux N, Fruchart JC, Amouyel P. Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis. *J Nutr* 1998; **128**: 1450-1457 [PMID: 9732304]
92 **Forastiere F**, Mallone S, Lo Presti E, Baldacci S, Pistelli F, Simoni M, Scalera A, Pedreschi M, Pistelli R, Corbo G, Rapiti E, Agabiti N, Farchi S, Basso S, Chiaffi L, Matteelli G, Di Pede F, Carrozzi L, Viegi G. Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas. *Environ Health Perspect* 2000; **108**: 1171-1177 [PMID: 11133398 DOI: 10.1289/ehp.001081171]
93 **Iribarren C**, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. *J Epidemiol Community Health* 2001; **55**: 721-728 [PMID: 11553655 DOI: 10.1136/jech.55.10.721]
94 **Connor Gorber S**, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine Tob Res* 2009; **11**: 12-24 [PMID: 19246437 DOI: 10.1093/ntr/ntn010]
95 **Lehnert G**, Garfinkel L, Hirayama T, Schmähl D, Uberla K, Wynder EL, Lee P. Roundtable discussion: symposium: medical perspectives on passive smoking. *Prev Med* 1984; **13**: 730-746 [PMID: 6536947]
96 **England LJ**, Grauman A, Qian C, Wilkins DG, Schisterman EF, Yu KF, Levine RJ. Misclassification of maternal smoking status and its effects on an epidemiologic study of pregnancy outcomes. *Nicotine Tob Res* 2007; **9**: 1005-1013 [PMID: 17852766 DOI: 10.1080/14622200701491255]
97 **Jung-Choi KH**, Khang YH, Cho HJ. Hidden female smokers in Asia: a comparison of self-reported with cotinine-verified smoking prevalence rates in representative national data from an Asian population. *Tob Control* 2012; **21**: 536-542 [PMID: 21972062 DOI: 10.1136/tobaccocontrol-2011-050012]
98 **Sterling TD**. Publication decisions and their possible effects on inferences drawn from tests of significance - or vice versa. *J Am Stat Assoc* 1959; **54**: 30-34 [DOI: 10.2307/2282137]
99 **Begg CB**, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101 [PMID: 7786990 DOI: 10.2307/2533446]
100 **Easterbrook PJ**, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**: 867-872 [PMID: 1672966 DOI: 10.1016/0140-6736(91)90201-Y]
101 **Lee PN**. Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer. A review of the published data. *APMIS* 1994; **102** Suppl 45: 4
102 **Faccini JM**. The role of histopathology in the evaluation of risk of lung cancer from environmental tobacco smoke. *Exp Pathol* 1989; **37**: 177-180 [PMID: 2637150 DOI: 10.1016/S0232-1513(89)80042-8]
103 **Sterling TD**, Rosenbaum WL, Weinkam JJ. Bias in the attribution of lung cancer as cause of death and its possible consequences for calculating smoking-related risks. *Epidemiology* 1992; **3**: 11-16 [PMID: 1554804 DOI: 10.1097/00001648-199201000-00004]
104 **Hammond EC**. Smoking in relation to the death rates of one million men and women. In: Haenszel W, editor. Epidemiological approaches to the study of cancer and other chronic diseases. Bethesda, Maryland: U.S. Department of Health, Education, and Welfare. Public Health Service National Cancer Institute, 1966: 127-204
105 **Chan WC**, Fung SC. Lung cancer in non-smokers in Hong Kong. In: Grundmann E, editor. Cancer Epidemiology. Volume 6. Stuttgart, New York: Gustav Fischer Verlag, 1982: 199-202
106 **Chan WC**, Colbourne MJ, Fung SC, Ho HC. Bronchial cancer in Hong Kong 1976-1977. *Br J Cancer* 1979; **39**: 182-192 [PMID: 435367 DOI: 10.1038/bjc.1979.29]
107 **Chan WC**. Zahlen aus Hongkong. *Munch Med Wochenschr* 1982; **124**: 16
108 **Trichopoulos D**, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981; **27**: 1-4 [PMID: 7251227 DOI: 10.1002/ijc.2910270102]
109 **Trichopoulos D**, Kalandidi A, Tzonou A. Incidence and distribution of lung cancer in Greece. *Excerpta Medica International Congress Series* 1982; **558**: 10-17
110 **Buffler PA**, Pickle LW, Mason TJ, Contant C. The causes of lung cancer in Texas. In: Mizell M, Correa P, editors. Lung cancer: causes and prevention, Proceedings of the International Lung Cancer Update Conference, New Orleans, Louisiana, March 3-5, 1983. Deerfield Beach, Florida: Verlag Chemie International, Inc, 1984: 83-99
111 **Hirayama T**. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* (Clin

Res Ed) 1981; **282**: 183-185 [PMID: 6779940 DOI: 10.1136/bmj.282.6259.183]
112 **Hirayama T**. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 1984; **13**: 680-690 [PMID: 6536942 DOI: 10.1016/S0091-7435(84)80017-1]
113 **Hirayama T**. Passive smoking--a new target of epidemiology. *Tokai J Exp Clin Med* 1985; **10**: 287-293 [PMID: 3836507]
114 **Hirayama T**. Passive smoking and cancer: an epidemiological review. In: Aoki K, Kurihara M, Miller W, Muir CS, editors. Changing cancer patterns and topics in cancer epidemiology. In Memory of Professor Mitsuo Segi. Volume 33. Basel, Switzerland: S. Karger AG, 1987: 127-135
115 **Hirayama T**. Health effects of active and passive smoking. In: Aoki M, Hisamichi S, Tominaga S, editors. Smoking and health 1987, Proceedings of the 6th World Conference on Smoking and Health, Tokyo, 9-12 November 1987. Amsterdam: Elsevier Science Publishers B.V. (Biomedical Division), 1988: 75-86
116 **Hirayama T**. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. *Cancer Chemother Pharmacol* 1989; **23** Suppl: S114-S117 [PMID: 2924384 DOI: 10.1007/BF00647254]
117 **Hirayama T**. Dietary habits are of limited importance in influencing the lung cancer risk among Japanese females who never smoked. In: Bieva CJ, Courtois Y, Govaerts M, editors. Present and future of indoor air quality, Proceedings of the Brussels Conference, 14-16 February 1989. Amsterdam: Elsevier Science Publishers BV (Biomedical Division), 1989: 77-82
118 **Hirayama T**. Life-style and mortality: A large scale census based cohort study in Japan. Volume 6. Basel, Switzerland: Karger, 1990
119 **Hirayama T**. Passive smoking and cancer: The association between husbands smoking and cancer in the lung of non-smoking wives. In: Kasuga H, editor. Indoor air quality, International Conference on Indoor Air Quality, Tokyo, November 4-6, 1987. Berlin Heidelberg: Springer-Verlag, 1990: 299-311
120 **Hirayama T**. Lung cancer and other diseases related to passive smoking: a large-scale cohort study. In: Gupta PC, Hamner JE, III, Murti PR, editors. Control of tobacco-related cancers and other diseases. Bombay: Oxford University Press, 1992: 129-127
121 **Garfinkel L**, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. *J Natl Cancer Inst* 1985; **75**: 463-469 [PMID: 3861899 DOI: 10.1093/jnci/75.3.463]
122 **Stellman SD**, Garfinkel L. Passive smoking and lung cancer: An American Cancer Society study. In: Kasuga H, editor. Indoor air quality, International Conference on Indoor Air Quality, Tokyo, November 4-6, 1987. Berlin Heidelberg: Springer-Verlag, 1990: 283-289
123 **Wu AH**, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. *J Natl Cancer Inst* 1985; **74**: 747-751 [PMID: 3857370 DOI: 10.1093/jnci/74.4.747]
124 **Lee PN**, Chamberlain J, Alderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br J Cancer* 1986; **54**: 97-105 [PMID: 3730259 DOI: 10.1038/bjc.1986.157]
125 **Brownson RC**, Reif JS, Keefe TJ, Ferguson SW, Pritzl JA. Risk factors for adenocarcinoma of the lung. *Am J Epidemiol* 1987; **125**: 25-34 [PMID: 3788953]
126 **Gao YT**, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, Zhang R, Fraumeni JF. Lung cancer among Chinese women. *Int J Cancer* 1987; **40**: 604-609 [PMID: 2824385 DOI: 10.1002/ijc.2910400505]
127 **Humble CG**, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. *Am J Public Health* 1987; **77**: 598-602 [PMID: 3565655 DOI: 10.2105/AJPH.77.5.598]
128 **Koo LC**, Ho JH, Saw D, Ho CY. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *Int J Cancer* 1987; **39**: 162-169 [PMID: 3804491 DOI: 10.1002/ijc.2910390207]
129 **Koo LC**, Ho JH-C, Saw D. Active and passive smoking among female lung cancer patients and controls in Hong Kong. *J Exp Clin Cancer Res* 1983; **4**: 367-375
130 **Koo LC**, Ho JH-C, Saw D. Is passive smoking an added risk factor for lung cancer in Chinese women? *J Exp Clin Cancer Res* 1984; **3**: 277-283
131 **Koo LC**, Ho JH, Lee N. An analysis of some risk factors for lung cancer in Hong Kong. *Int J Cancer* 1985; **35**: 149-155 [PMID: 3972468 DOI: 10.1002/ijc.2910350202]
132 **Koo LC**, Ho JH, Rylander R. Life-history correlates of environmental tobacco smoke: a study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. *Soc Sci Med* 1988; **26**: 751-760 [PMID: 3358146]
133 **Koo LC**, Ho JH. Diet as a confounder of the association between air pollution and female lung cancer: Hong Kong studies on exposures to environmental tobacco smoke, incense, and cooking fumes as examples. *Lung Cancer* 1996; **14** Suppl 1: S47-S61 [PMID: 8785667 DOI: 10.1016/S0169-5002(96)90210-X]
134 **Pershagen G**, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol* 1987; **125**: 17-24 [PMID: 3788950]
135 **Pershagen G**, Svensson C, Hrubec Z. Environmental tobacco smoke and lung cancer in Swedish women. In: Seifert B, Esdorn H, Fischer M, Rüden H, Wegner J, editors. Indoor Air 87, Volume 2, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Berlin (West), 17-21 August 1987. Berlin: Institute for Water, Soil and Air Hygiene, 1988: 34-38
136 **Butler TL**. The relationship of passive smoking to various health outcomes among Seventh day Adventists in California [Thesis]. Los Angeles: University of California, 1988
137 **Geng G**, Liang Z, Xu R, Liu J, Shi P. The relationship between smoking and lung cancer in humans. In: International symposium on lifestyle factors and human lung cancer. Dec 12-16 1994, Guangzhou, People's Republic of China. 1994: 1-8
138 **Inoue R**, Hirayama T. Passive smoking and lung cancer in women. In: Aoki M, Hisamichi S, Tominaga S, editors. Smoking and health 1987, Proceedings of the 6th World Conference on Smoking and Health, Tokyo, 9-12 November 1987. Amsterdam: Elsevier Science Publishers B.V. (Biomedical Division), 1988: 283-285
139 **Choi SY**, Lee KH, Lee TO. A case-control study on risk factors in lung cancer. *Korean J Epidemiol* 1989; **11**: 66-80
140 **Hole DJ**, Gillis CR, Chopra C, Hawthorne VM. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *BMJ* 1989; **299**: 423-427 [PMID: 2507000 DOI: 10.1136/bmj.299.6696.423]
141 **Gillis CR**, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Respir Dis Suppl* 1984; **133**: 121-126 [PMID: 6586460 DOI: 10.1016/j.ypmed.2007.11.016]
142 **Schoenberg J**, Klotz J. A case-control study of radon and lung cancer among New Jersey women. USA: New Jersey State Department of Health, 1989 Technical report - phase I. Available from: URL: http//www.state.nj.us/health/eohs/regional_state/air/case_control_women.pdf
143 **Svensson C**, Pershagen G, Klominek J. Smoking and passive smoking in relation to lung cancer in women. *Acta Oncol* 1989; **28**: 623-629 [PMID: 2590538 DOI: 10.3109/02841868909092282]
144 **Svensson C**. Lung cancer etiology in women [Thesis]. Stockholm: Departments of Oncology and Environmental Hygiene, Karolinska Institute, 1988
145 **Varela LR**. Assessment of the association between passive smoking and lung cancer [Thesis]. New Haven, Conn: Faculty of the Graduate School of Yale University, 1987
146 **Sobue T**. Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *Int J Epidemiol* 1990; **19** Suppl 1: S62-S66 [PMID: 2258278 DOI: 10.1093/ije/19.Supplement_1.S62]
147 **Sobue T**, Suzuki R, Nakayama N, Inubuse C, Matsuda M, Doi O, Mori T, Furuse K, Fukuoka M, Yasumitsu T, Kuwabara O, Ichigaya M, Kurata M, Kuwabara M, Nakahara K, Endo S, Hattori S. Passive smoking smong nonsmoking women and the relationship between indoor air pollution and lung cancer incidence - results of a multicenter case controlled study. *Gan No Rinsho* 1990; **36**: 329-333
148 **Liu ZY**, He XZ, Chapman RS. Smoking and other risk factors for

lung cancer in Xuanwei, China. *Int J Epidemiol* 1991; **20**: 26-31 [PMID: 2066232 DOI: 10.1093/ije/20.1.26]
149 **Liu Z**. [A case-control study of lung cancer risk factors in Xuanwei]. *Zhonghua Liu Xing Bing Xue Za Zhi* 1990; **11**: 79-83 [PMID: 2372823]
150 **He XZ**, Chen W, Liu ZY, Chapman RS. An epidemiological study of lung cancer in Xuan Wei County, China: current progress. Case-control study on lung cancer and cooking fuel. *Environ Health Perspect* 1991; **94**: 9-13 [PMID: 1954946 DOI: 10.2307/3431286]
151 **Brownson RC**, Alavanja MC, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. *Am J Public Health* 1992; **82**: 1525-1530 [PMID: 1443304 DOI: 10.2105/AJPH.82.11.1525]
152 **Butler WJ**. Workplace exposure to ETS and lung cancer: a more detailed presentation of the data from a negative study, Brownson et al (1992). Washington DC: Occupational Safety and Health Administration, 1994
153 **Alavanja MCR**, Brownson RC, Benichou J, Swanson C, Boice JD, Jr. Attributable risk of lung cancer in nonsmoking women. In: International symposium on lifestyle factors and human lung cancer. Guangzhou, People's Republic of China. 1994: 1-13
154 **Alavanja MC**, Brownson RC, Benichou J, Swanson C, Boice JD. Attributable risk of lung cancer in lifetime nonsmokers and long-term ex-smokers (Missouri, United States). *Cancer Causes Control* 1995; **6**: 209-216 [PMID: 7612800]
155 **Bennett WP**, Alavanja MC, Blomeke B, Vähäkangas KH, Castrén K, Welsh JA, Bowman ED, Khan MA, Flieder DB, Harris CC. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. *J Natl Cancer Inst* 1999; **91**: 2009-2014 [PMID: 10580025 DOI: 10.1093/jnci/91.23.2009]
156 **Stockwell HG**, Candelora EC, Armstrong AW, Pinkham PA. Environmental tobacco smoke and lung cancer in never smoking women. *Am J Epidemiol* 1991; **134**: 724
157 **Du Y**, Cha Q, Chen X, Chen Y, Lei Y, Xue S. Exposure to environmental tobacco smoke and female lung cancer. *Indoor Air* 1995; **5**: 231-236 [DOI: 10.1111/j.1600-0668.1995.00002.x]
158 **Laux G**, Madirazza D. [Follow-up studies of surgery for varicoses veins. Psychological and surgical aspects]. *ZFA* (Stuttgart) 1977; **53**: 741-744 [PMID: 878567 DOI: 10.1016/S0169-5002(96)90208-1]
159 **Lei YX**, Cai WC, Chen YZ, Du YX. Some lifestyle factors in human lung cancer: a case-control study of 792 lung cancer cases. *Lung Cancer* 1996; **14** Suppl 1: S121-S136 [PMID: 8785658 DOI: 10.1016/S0169-5002(96)90218-4]
160 **Liu Q**, Sasco AJ, Riboli E, Hu MX. Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. *Am J Epidemiol* 1993; **137**: 145-154 [PMID: 8452118]
161 **Fontham ET**, Correa P, WuWilliams A, Reynolds P, Greenberg RS, Buffler PA, Chen VW, Boyd P, Alterman T, Austin DF. Lung cancer in nonsmoking women: a multicenter case-control study. *Cancer Epidemiol Biomarkers Prev* 1991; **1**: 35-43 [PMID: 1845167]
162 **Fontham ETH**, Correa P, Buffler PA, Greenberg R, Reynolds P, Wu-Williams A. Environmental tobacco smoke and lung cancer. *Cancer Bull* 1993; **45**: 92-94
163 **Fontham ET**, Correa P, Chen VW. Passive smoking and lung cancer. *J La State Med Soc* 1993; **145**: 132-136 [PMID: 8486984]
164 **Reynolds P**, von Behren J, Fontham ET, Correa P, Wu A, Buffler PA, Greenberg RS. Occupational exposure to environmental tobacco smoke. *JAMA* 1996; **275**: 441-442 [PMID: 8627956 DOI: 10.1001/jama.1996.03530300025019]
165 **Layard MW**. Ischemic heart disease, lung cancer, and spousal smoking in the National Mortality Followback Survey. Submitted to OSHA re Proposed Rules. *Federal Register* 1994; **59**: 65, Docket No H-122
166 **de Waard F**, Kemmeren JM, van Ginkel LA, Stolker AA. Urinary cotinine and lung cancer risk in a female cohort. *Br J Cancer* 1995; **72**: 784-787 [PMID: 7669595 DOI: 10.1038/bjc.1995.411]
167 **Ellard GA**, de Waard F, Kemmeren JM. Urinary nicotine metabolite excretion and lung cancer risk in a female cohort. *Br J Cancer* 1995; **72**: 788-791 [PMID: 7669596 DOI: 10.1038/bjc.1995.412]
168 **Kabat GC**, Stellman SD, Wynder EL. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *Am J Epidemiol* 1995; **142**: 141-148 [PMID: 7598113]
169 **Kabat GC**. Epidemiologic studies of the relationship between passive smoking and lung cancer. In: Presented at the 1990 annual winter meeting of the Toxicology Forum in Washington, DC. 1990: 187-199
170 **Kabat GC**. Aspects of the epidemiology of lung cancer in smokers and nonsmokers in the United States. In: International symposium on lifestyle factors and human lung cancer. Dec 12-16 1994, Guangzhou, People's Republic of China. 1994: 1-27
171 **Wang TJ**, Zhou BS, Shi JP. Lung cancer in nonsmoking Chinese women: a case-control study. *Lung Cancer* 1996; **14** Suppl 1: S93-S98 [PMID: 8785672 DOI: 10.1016/S0169-5002(96)90214-7]
172 **Cardenas VM**. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II [Thesis]. Atlanta, Georgia: Emory University, 1994
173 **Cardenas VM**. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II. *Diss Abstr Int* 1995; **56/07-B**: 3714
174 **Auvinen A**, Mäkeläinen I, Hakama M, Castrén O, Pukkala E, Reisbacka H, Rytömaa T. Indoor radon exposure and risk of lung cancer: a nested case-control study in Finland. *J Natl Cancer Inst* 1996; **88**: 966-972 [PMID: 8667427 DOI: 10.1093/jnci/88.14.966]
175 **Boffetta P**, Brennan S, Lea S, Ferro G. Lung cancer and exposure to environmental tobacco smoke. IARC biennial report. In: IARC, 1998: 76-77
176 **Boffetta P**, Garcia-Gómez M, Pompe-Kirn V, Zaridze D, Bellander T, Bulbulyan M, Caballero JD, Ceccarelli F, Colin D, Dizdarevic T, Español S, Kobal A, Petrova N, Sällsten G, Merler E. Cancer occurrence among European mercury miners. *Cancer Causes Control* 1998; **9**: 591-599 [PMID: 10189044 DOI: 10.1023/A:1008849208686]
177 **Boffetta P**, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jöckel KH, Krauss M, Kreienbrock L, Kreuzer M, Mendes A, Merletti F, Nyberg F, Pershagen G, Pohlabeln H, Riboli E, Schmid G, Simonato L, Trédaniel J, Whitley E, Wichmann H-E, Winck C, Zambon P, Saracci R. European multicentre case-control study of lung cancer in non-smokers. Detailed results on exposure to environmental tobacco smoke. Lyon: International Agency for Research on Cancer, 1998
178 **Boffetta P**, Nyberg F, Agudo A, Benhamou E, Jockel KH, Kreuzer M, Merletti F, Pershagen G, Pohlabeln H, Simonato L, Wichmann HE, Saracci R. Risk of lung cancer from exposure to environmental tobacco smoke from cigars, cigarillos and pipes. *Int J Cancer* 1999; **83**: 805-806 [PMID: 10597199 DOI: 10.1002/(SICI)1097-0215(19991210)83]
179 **Brennan P**, Butler J, Agudo A, Benhamou S, Darby S, Fortes C, Jöckel KH, Kreuzer M, Nyberg F, Pohlabeln H, Saracci R, Wichman HE, Boffetta P. Joint effect of diet and environmental tobacco smoke on risk of lung cancer among nonsmokers. *J Natl Cancer Inst* 2000; **92**: 426-427 [PMID: 10699073 DOI: 10.1093/jnci/92.5.426]
180 **Kreuzer M**, Krauss M, Kreienbrock L, Jöckel KH, Wichmann HE. Environmental tobacco smoke and lung cancer: a case-control study in Germany. *Am J Epidemiol* 2000; **151**: 241-250 [PMID: 10670548 DOI: 10.1093/oxfordjournals.aje.a010199]
181 **Shen XB**, Wang GX, Zhou BS. Relation of exposure to environmental tobacco smoke and pulmonary adenocarcinoma in non-smoking women: a case control study in Nanjing. *Oncol Rep* 1998; **5**: 1221-1223 [PMID: 9683839 DOI: 10.3892/or.5.5.1221]
182 **Shen X**, Wang G, Xiang L, Huang Y. Analyses of sex differentials in risk factors for primary lung adenocarcinoma. In: International symposium on lifestyle factors and human lung cancer, International symposium on lifestyle factors and human lung cancer. Guangzhou, People's Republic of China. 1994: 1-6
183 **Shen XB**, Wang GX, Huang YZ, Xiang LS, Wang XH. Analysis and estimates of attributable risk factors for lung cancer in Nanjing, China. *Lung Cancer* 1996; **14** Suppl 1: S107-S112 [PMID: 8785656 DOI: 10.1016/S0169-5002(96)90216-0]
184 **Shen XB**, Wang GX, Xiang LS, Huang YZ. International Symposium on Lifestyle Factors and Human Lung Cancer. Guangzhou, China, 12-16 December 1994. Proceedings and

abstracts. *Lung Cancer* 1996; **14** Suppl 1: S1-245 [PMID: 8785655]
185 **Shen X**, Wang G, Xiang L, Wu JM. Relationship of passive smoking and pulmonary adenocarcinoma in non-smoking women - a case control study in Nanjing, P.R. China. *Epidemiology* 1996; **7**: S20 [DOI: 10.1097/00001648-199607001-00008]
186 **Zaridze DG**, Zemlyanaya GM. Indoor air pollution and lung cancer risk in non-smoking women in Moscow. *Exp Oncol* 1994; **16**: 441-445
187 **Zaridze D**. Indoor and outdoor air pollution and the risk of lung cancer. *Epidemiology* 1998; **9** (Suppl): S90
188 **Zemlianaja GM**, Zaridze DG. Lung cancer in non-smoking women in Moscow. *Epidemiology* 1998; **9** (Suppl): S89
189 **Boffetta P**, Ahrens W, Nyberg F, Mukeria A, Brüske-Hohlfeld I, Fortes C, Constantinescu V, Simonato L, Batura-Gabryel H, Lea S, Gaborieau V, Benhamou S. Exposure to environmental tobacco smoke and risk of adenocarcinoma of the lung. *Int J Cancer* 1999; **83**: 635-639 [PMID: 10521800 DOI: 10.1002/(SICI)1097-0215(19991126)83]
190 **Jee SH**, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* 1999; **28**: 824-828 [PMID: 10597977 DOI: 10.1093/ije/28.5.824]
191 **Speizer FE**, Colditz GA, Hunter DJ, Rosner B, Hennekens C. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). *Cancer Causes Control* 1999; **10**: 475-482 [PMID: 10530619 DOI: 10.1023/A: 1008931526525]
192 **Ko YC**, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, Wang HZ, Chang PY. Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int J Epidemiol* 1997; **26**: 24-31 [PMID: 9126500 DOI: 10.1093/ije/26.1.24]
193 **Ko YC**, Cheng LS, Lee CH, Huang JJ, Huang MS, Kao EL, Wang HZ, Lin HJ. Chinese food cooking and lung cancer in women nonsmokers. *Am J Epidemiol* 2000; **151**: 140-147 [PMID: 10645816 DOI: 10.1093/oxfordjournals.aje.a010181]
194 **Lee PN**. A review of the epidemiology of heart disease related to active smoking. The role of amount smoked, age and time quit smoking. Sutton, Surrey: P N Lee Statistics and Computing Ltd, 2001. Available from: URL: http//www.pnlee.co.uk/Reports.htm
195 **Malats N**, Camus-Radon AM, Nyberg F, Ahrens W, Constantinescu V, Mukeria A, Benhamou S, Batura-Gabryel H, Bruske-Hohlfeld I, Simonato L, Menezes A, Lea S, Lang M, Boffetta P. Lung cancer risk in nonsmokers and GSTM1 and GSTT1 genetic polymorphism. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 827-833 [PMID: 10952100]
196 **Cohet C**, Borel S, Nyberg F, Mukeria A, Brüske-Hohlfeld I, Constantinescu V, Benhamou S, Brennan P, Hall J, Boffetta P. Exon 5 polymorphisms in the O6-alkylguanine DNA alkyltransferase gene and lung cancer risk in non-smokers exposed to second-hand smoke. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 320-323 [PMID: 14973087 DOI: 10.1158/1055-9965.EPI-03-0120]
197 **Kleinerman RA**, Wang ZY, Lubin JH, Zhang SZ, Metayer C, Brenner AV. Lung cancer and indoor air pollution in rural China. *Ann Epidemiol* 2000; **10**: 469
198 **Johnson KC**, Hu J, Mao Y. 1-800-AIDS-NIH. *Science* 1992; **257**: 1207 [PMID: 1519055 DOI: 10.1002/ijc.1416]
199 **Johnson KC**, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994-97. *Cancer Causes Control* 2000; **11**: 211-221 [PMID: 10782655]
200 **Johnson KC**, Hu J, Mao Y. Lifetime workplace and residential exposure to environmental tobacco smoke and lung cancer in never-smoking women. *Am J Epidemiol* 2000; **151** (Suppl): S28
201 **Hu J**, Mao Y, Dryer D, White K. Risk factors for lung cancer among Canadian women who have never smoked. *Cancer Detect Prev* 2002; **26**: 129-138 [PMID: 12102147 DOI: 10.1016/S0361-090X(02)00038-7]
202 **Lagarde F**, Axelsson G, Damber L, Mellander H, Nyberg F, Pershagen G. Residential radon and lung cancer among never-smokers in Sweden. *Epidemiology* 2001; **12**: 396-404 [PMID: 11416777]
203 **Hou SM**, Yang K, Nyberg F, Hemminki K, Pershagen G, Lambert B. Hprt mutant frequency and aromatic DNA adduct level in non-smoking and smoking lung cancer patients and population controls. *Carcinogenesis* 1999; **20**: 437-444 [PMID: 10190559 DOI: 10.1093/carcin/20.3.437]
204 **Nishino Y**, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control* 2001; **12**: 797-802 [PMID: 11714107 DOI: 10.1023/A: 1012273806199]
205 **Ohno Y**, Wakai K, Ando M, Shimokata K, Saka H, Yamamoto M, Shima K, Sugiura S, Sakai S, Nomura F, Watanabe A. Studies on health effects of passive smoking - multicancer case-control study of the relationship between passive smoking and lung cancer in lifetime nonsmokers. In: SRF Annual Report 2001. 2002: 857-861
206 **Rachtan J**. A case-control study of lung cancer in Polish women. *Neoplasma* 2002; **49**: 75-80 [PMID: 12088109]
207 **Enstrom JE**, Kabat GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003; **326**: 1057 [PMID: 12750205 DOI: 10.1136/bmj.326.7398.1057]
208 **Enstrom JE**, Heath CW. Smoking cessation and mortality trends among 118,000 Californians, 1960-1997. *Epidemiology* 1999; **10**: 500-512 [PMID: 10468422 DOI: 10.1097/00001648-199909000-00007]
209 **Kubík A**, Zatloukal P, Boyle P, Robertson C, Gandini S, Tomásek L, Gray N, Havel L. A case-control study of lung cancer among Czech women. *Lung Cancer* 2001; **31**: 111-122 [PMID: 11165390 DOI: 10.1016/S0169-5002(00)00178-1]
210 **Kubík AK**, Zatloukal P, Tomásek L, Petruzelka L. Lung cancer risk among Czech women: a case-control study. *Prev Med* 2002; **34**: 436-444 [PMID: 11914050 DOI: 10.1006/pmed.2001.100.1002]
211 **McGhee SM**, Ho SY, Schooling M, Ho LM, Thomas GN, Hedley AJ, Mak KH, Peto R, Lam TH. Mortality associated with passive smoking in Hong Kong. *BMJ* 2005; **330**: 287-288 [PMID: 15677632 DOI: 10.1136/bmj.38342.706748.47]
212 **Vineis P**, Airoldi L, Veglia F, Olgiati L, Pastorelli R, Autrup H, Dunning A, Garte S, Gormally E, Hainaut P, Malaveille C, Matullo G, Peluso M, Overvad K, Tjonneland A, Clavel-Chapelon F, Boeing H, Krogh V, Palli D, Panico S, Tumino R, Bueno-De-Mesquita B, Peeters P, Berglund G, Hallmans G, Saracci R, Riboli E. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. *BMJ* 2005; **330**: 277 [PMID: 15681570 DOI: 10.1136/bmj.38327.648472.82]
213 **Vineis P**, Anttila S, Benhamou S, Spinola M, Hirvonen A, Kiyohara C, Garte SJ, Puntoni R, Rannug A, Strange RC, Taioli E. Evidence of gene gene interactions in lung carcinogenesis in a large pooled analysis. *Carcinogenesis* 2007; **28**: 1902-1905 [PMID: 17307802 DOI: 10.1093/carcin/bgm039]
214 **Vineis P**, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund E E, Agudo A, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Manjer J, Forsberg B, Day NE, Key TJ, Kaaks R, Saracci R, Riboli E. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 2007; **6**: 7 [PMID: 17302981 DOI: 10.1186/1476-069X-6-7]
215 **Veglia F**, Vineis P, Overvad K, Boeing H, Bergmann M, Trichopoulou A, Trichopoulos D, Palli D, Krogh V, Tumino R, Linseisen J, Steindorf K, Raaschou-Nielsen O, Tjonneland A, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Day NE, Saracci R, Riboli E. Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology* 2007; **18**: 769-775 [PMID: 18062064]
216 **International Agency for Research on Cancer**. IARC Handbooks of Cancer Prevention, Tobacco Control, Vol 13: Evaluating the effectiveness of smoke-free policies. Lyon, France: IARC, 2009
217 **Hudmon KS**, Honn SE, Jiang H, Chamberlain RM, Xiang W, Ferry G, Gosbee W, Hong WK, Spitz MR. Identifying and recruiting healthy control subjects from a managed care organization: a methodology for molecular epidemiological case-control studies of cancer. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 565-571

[PMID: 9264268]
218 **Gorlova OY**, Weng SF, Zhang Y, Amos CI, Spitz MR, Wei Q. DNA repair capacity and lung cancer risk in never smokers. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 1322-1328 [PMID: 18559546 DOI: 10.1158/1055-9965.EPI-07-2591]
219 **Spitz MR**, Wei Q, Dong Q, Amos CI, Wu X. Genetic susceptibility to lung cancer: the role of DNA damage and repair. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 689-698 [PMID: 12917198]
220 **Spitz MR**, Hong WK, Amos CI, Wu X, Schabath MB, Dong Q, Shete S, Etzel CJ. A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007; **99**: 715-726 [PMID: 17470739 DOI: 10.1093/jnci/djk153]
221 **Spitz MR**, Gorlov IP, Amos CI, Dong Q, Chen W, Etzel CJ, Gorlova OY, Chang DW, Pu X, Zhang D, Wang L, Cunningham JM, Yang P, Wu X. Variants in inflammation genes are implicated in risk of lung cancer in never smokers exposed to second-hand smoke. *Cancer Discov* 2011; **1**: 420-429 [PMID: 22586632 DOI: 10.1158/2159-8290.CD-11-0080]
222 **Gorlova OY**, Weng SF, Hernandez L, Spitz MR, Forman MR. Dietary patterns affect lung cancer risk in never smokers. *Nutr Cancer* 2011; **63**: 842-849 [PMID: 21774612 DOI: 10.1080/01635581.2011.589958]
223 **Rylander R**, Axelsson G. Lung cancer risks in relation to vegetable and fruit consumption and smoking. *Int J Cancer* 2006; **118**: 739-743 [PMID: 16108070 DOI: 10.1002/ijc.21384]
224 **Zheng W**, Chow WH, Yang G, Jin F, Rothman N, Blair A, Li HL, Wen W, Ji BT, Li Q, Shu XO, Gao YT. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005; **162**: 1123-1131 [PMID: 16236996 DOI: 10.1093/aje/kwi322]
225 **Weiss JM**, Lacey JV, Shu XO, Ji BT, Hou L, Yang G, Li H, Rothman N, Blair A, Gao YT, Chow WH, Zheng W. Menstrual and reproductive factors in association with lung cancer in female lifetime nonsmokers. *Am J Epidemiol* 2008; **168**: 1319-1325 [PMID: 18849300 DOI: 10.1093/aje/kwn257]
226 **Pronk A**, Coble J, Ji BT, Shu XO, Rothman N, Yang G, Gao YT, Zheng W, Chow WH. Occupational risk of lung cancer among lifetime non-smoking women in Shanghai, China. *Occup Environ Med* 2009; **66**: 672-678 [PMID: 19625285 DOI: 10.1136/oem.2008.043695]
227 **Fowke JH**, Gao YT, Chow WH, Cai Q, Shu XO, Li HL, Ji BT, Rothman N, Yang G, Chung FL, Zheng W. Urinary isothiocyanate levels and lung cancer risk among non-smoking women: a prospective investigation. *Lung Cancer* 2011; **73**: 18-24 [PMID: 21122939 DOI: 10.1016/j.lungcan.2010.10.024]
228 **Yu IT**, Chiu YL, Au JS, Wong TW, Tang JL. Dose-response relationship between cooking fumes exposures and lung cancer among Chinese nonsmoking women. *Cancer Res* 2006; **66**: 4961-4967 [PMID: 16651454 DOI: 10.1158/0008-5472.CAN-05-2932]
229 **Wang XR**, Chiu YL, Qiu H, Au JS, Yu IT. The roles of smoking and cooking emissions in lung cancer risk among Chinese women in Hong Kong. *Ann Oncol* 2009; **20**: 746-751 [PMID: 19150939 DOI: 10.1093/annonc/mdn699]
230 **Chiu YL**, Wang XR, Qiu H, Yu IT. Risk factors for lung cancer: a case-control study in Hong Kong women. *Cancer Causes Control* 2010; **21**: 777-785 [PMID: 20084541 DOI: 10.1007/s10552-010-9506-9]
231 **Hill SE**, Blakely T, Kawachi I, Woodward A. Mortality among lifelong nonsmokers exposed to secondhand smoke at home: cohort data and sensitivity analyses. *Am J Epidemiol* 2007; **165**: 530-540 [PMID: 17172631 DOI: 10.1093/aje/kwk043]
232 **López-Cima MF**, González-Arriaga P, García-Castro L, Pascual T, Marrón MG, Puente XS, Tardón A. Polymorphisms in XPC, XPD, XRCC1, and XRCC3 DNA repair genes and lung cancer risk in a population of northern Spain. *BMC Cancer* 2007; **7**: 162 [PMID: 17705814 DOI: 10.1186/1471-2407-7-162]
233 **Asomaning K**, Miller DP, Liu G, Wain JC, Lynch TJ, Su L, Christiani DC. Second hand smoke, age of exposure and lung cancer risk. *Lung Cancer* 2008; **61**: 13-20 [PMID: 18191495 DOI: 10.1016/j.lungcan.2007.11.013]
234 **Kurahashi N**, Inoue M, Liu Y, Iwasaki M, Sasazuki S, Sobue T, Tsugane S. Passive smoking and lung cancer in Japanese non-smoking women: a prospective study. *Int J Cancer* 2008; **122**: 653-657 [PMID: 17935128 DOI: 10.1002/ijc.23116]
235 **Yang P**, Wentzlaff KA, Katzmann JA, Marks RS, Allen MS, Lesnick TG, Lindor NM, Myers JL, Wiegert E, Midthun DE, Thibodeau SN, Krowka MJ. Alpha1-antitrypsin deficiency allele carriers among lung cancer patients. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 461-465 [PMID: 10350443]
236 **Yang P**, Allen MS, Aubry MC, Wampfler JA, Marks RS, Edell ES, Thibodeau S, Adjei AA, Jett J, Deschamps C. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest* 2005; **128**: 452-462 [PMID: 16002972 DOI: 10.1378/chest.128.1.452]
237 **Zheng YL**, Loffredo CA, Yu Z, Jones RT, Krasna MJ, Alberg AJ, Yung R, Perlmutter D, Enewold L, Harris CC, Shields PG. Bleomycin-induced chromosome breaks as a risk marker for lung cancer: a case-control study with population and hospital controls. *Carcinogenesis* 2003; **24**: 269-274 [PMID: 12584177 DOI: 10.1093/carcin/bgg106]
238 **Tse LA**, Yu IT, Au JS, Yu KS, Kwok KP, Qiu H, Wong TW. Environmental tobacco smoke and lung cancer among Chinese nonsmoking males: might adenocarcinoma be the culprit? *Am J Epidemiol* 2009; **169**: 533-541 [PMID: 19126588 DOI: 10.1093/aje/kwn385]
239 **Tse LA**, Yu IS, Au JS, Qiu H, Wang XR. Silica dust, diesel exhaust, and painting work are the significant occupational risk factors for lung cancer in nonsmoking Chinese men. *Br J Cancer* 2011; **104**: 208-213 [PMID: 21102581 DOI: 10.1038/sj.bjc.6606006]
240 **Chuang SC**, Gallo V, Michaud D, Overvad K, Tjønneland A, Clavel-Chapelon F, Romieu I, Straif K, Palli D, Pala V, Tumino R, Sacerdote C, Panico S, Peeters PH, Lund E, Gram IT, Manjer J, Borgquist S, Riboli E, Vineis P. Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European Prospective Investigation into Cancer and Nutrition. *Cancer Causes Control* 2011; **22**: 487-494 [PMID: 21279734 DOI: 10.1007/s10552-010-9723-2]
241 **Kiyohara C**, Horiuchi T, Takayama K, Nakanishi Y. Methylenetetrahydrofolate reductase polymorphisms and interaction with smoking and alcohol consumption in lung cancer risk: a case-control study in a Japanese population. *BMC Cancer* 2011; **11**: 459 [PMID: 22024018 DOI: 10.1186/1471-2407-11-459]
242 **He Y**, Jiang B, Li LS, Li LS, Ko L, Wu L, Sun DL, He SF, Liang BQ, Hu FB, Lam TH. Secondhand smoke exposure predicted COPD and other tobacco-related mortality in a 17-year cohort study in China. *Chest* 2012; **142**: 909-918 [PMID: 22628493 DOI: 10.1378/chest.11-2884]
243 **Lam TH**, He Y, Li LS, Li LS, He SF, Liang BQ. Mortality attributable to cigarette smoking in China. *JAMA* 1997; **278**: 1505-1508 [PMID: 9363970 DOI: 10.1001/jama.1997.03550180055037]
244 **Zhao B**, Seow A, Lee EJ, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Yu MC, Lee HP. Dietary isothiocyanates, glutathione S-transferase -M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1063-1067 [PMID: 11588132 DOI: 10.1093/carcin/23.12.2055]
245 **Seow A**, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Chia KS, Yu MC, Lee HP. Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in nonsmokers. *Int J Cancer* 2002; **97**: 365-371 [PMID: 11774290 DOI: 10.1002/ijc.1615]
246 **Tang L**, Lim WY, Eng P, Leong SS, Lim TK, Ng AW, Tee A, Seow A. Lung cancer in Chinese women: evidence for an interaction between tobacco smoking and exposure to inhalants in the indoor environment. *Environ Health Perspect* 2010; **118**: 1257-1260 [PMID: 20472525 DOI: 10.1289/ehp.0901587]
247 **Ferreccio C**, Yuan Y, Calle J, Benítez H, Parra RL, Acevedo J, Smith AH, Liaw J, Steinmaus C. Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. *Epidemiology* 2013; **24**: 898-905 [PMID: 24036609 DOI: 10.1097/EDE.0b013e31829e3e03]

248 **Lo YL**, Hsiao CF, Jou YS, Chang GC, Tsai YH, Su WC, Chen YM, Huang MS, Chen HL, Yang PC, Chen CJ, Hsiung CA. ATM polymorphisms and risk of lung cancer among never smokers. *Lung Cancer* 2010; **69**: 148-154 [PMID: 20004998 DOI: 10.1016/j.lungcan.2009.11.007]

249 **Lo YL**, Hsiao CF, Jou YS, Chang GC, Tsai YH, Su WC, Chen KY, Chen YM, Huang MS, Hsieh WS, Chen CJ, Hsiung CA. Polymorphisms of MLH1 and MSH2 genes and the risk of lung cancer among never smokers. *Lung Cancer* 2011; **72**: 280-286 [PMID: 21093954 DOI: 10.1016/j.lungcan.2010.10.009]

250 **Hosseini M**, Naghan PA, Karimi S, SeyedAlinaghi S, Bahadori M, Khodadad K, Mohammadi F, Kaynama K, Masjedi MR. Environmental risk factors for lung cancer in Iran: a case-control study. *Int J Epidemiol* 2009; **38**: 989-996 [PMID: 19589809 DOI: 10.1093/ije/dyp218]

251 **Ren YW**, Yin ZH, Wan Y, Guan P, Wu W, Li XL, Zhou BS. P53 Arg72Pro and MDM2 SNP309 polymorphisms cooperate to increase lung adenocarcinoma risk in Chinese female non-smokers: a case control study. *Asian Pac J Cancer Prev* 2013; **14**: 5415-5420 [PMID: 24175836 DOI: 10.7314/APJCP.2013.14.9.5415]

252 **Seki T**, Nishino Y, Tanji F, Maemondo M, Takahashi S, Sato I, Kawai M, Minami Y. Cigarette smoking and lung cancer risk according to histologic type in Japanese men and women. *Cancer Sci* 2013; **104**: 1515-1522 [PMID: 23992614 DOI: 10.1111/cas.12273]

253 **Wang A**, Kubo J, Luo J, Desai M, Henderson MT, Chlebowski RT, Tindle H, Chen C, Manson JE, Schwartz AG, Cote ML, Wactawski-Wende J, Gomez SL, Patel MI, Stefanick ML, Wakelee HA. Active and passive smoking in relation to lung cancer incidence in the Women's Health Initiative prospective cohort study. *J Clin Oncol* 2013; **31** suppl: abstr 1504

254 **Kabat GC**, Kim M, Hunt JR, Chlebowski RT, Rohan TE. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. *Am J Epidemiol* 2008; **168**: 158-169 [PMID: 18483121 DOI: 10.1093/aje/kwn109]

255 **Torres-Durán M**, Ruano-Ravina A, Parente-Lamelas I, Leiro-Fernández V, Abal-Arca J, Montero-Martínez C, Pena-Álvarez C, González-Barcala FJ, Castro-Añón O, Golpe-Gómez A, Martínez C, Mejuto-Martí MJ, Fernández-Villar A, Barros-Dios JM. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). *Eur Respir J* 2014; **44**: 994-1001 [PMID: 25034571 DOI: 10.1183/09031936.00017114]

256 **Ruano-Ravina A**, García-Lavandeira JA, Torres-Durán M, Prini-Guadalupe L, Parente-Lamelas I, Leiro-Fernández V, Montero-Martínez C, González-Barcala FJ, Golpe-Gómez A, Martínez C, Castro-Añón O, Mejuto-Martí MJ, Barros-Dios JM. Leisure time activities related to carcinogen exposure and lung cancer risk in never smokers. A case-control study. *Environ Res* 2014; **132**: 33-37 [PMID: 24742725 DOI: 10.1016/j.envres.2014.03.027]

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META-ANALYSIS

Meta-analysis comparing differing methods of endoscopic therapy for colorectal lesions

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Abstract

AIM: To compare the outcomes of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of colorectal lesions.

METHODS: An electronic systematic literature search of four computerized databases was performed in July 2014 identifying studies reporting the outcomes of colorectal ESD and EMR. The primary outcome measures were *en-bloc* resection rate, endoscopic clearance rate and lesion recurrence rate of the patients followed up. The secondary outcome was the complication rate (including bleeding, perforation and surgery post EMR or ESD rate). Statistical pooling and random effects modelling of the studies calculating risk difference, heterogeneity and assessment of bias and quality were performed.

RESULTS: Six observational studies reporting the outcomes of 1324 procedures were included. The *en-bloc* resection rate was 50% higher in the ESD group than in the EMR group (95%CI: 0.17-0.83, $P < 0.0001$, $I^2 = 99.7\%$). Endoscopic clearance rates were also significantly higher in the ESD group (95%CI: -0.06-0.02, $P < 0.0001$, $I^2 = 92.5\%$). The perforation rate was 7% higher in the ESD group than the EMR group (95%CI: 0.05-0.09, $P > 0.05$, $I^2 = 41.1\%$) and the rate of recurrence was 50% higher in the EMR group than in the ESD group (95%CI: 0.20-0.79, $P < 0.001$, $I^2 = 99.5\%$). Heterogeneity remained consistent when subgroup analysis of high quality studies was performed (with the exception of piecemeal resection rate), and overall effect sizes remained unchanged for all outcomes.

CONCLUSION: ESD demonstrates higher *en-bloc* resection rates and lower recurrence rates compared to colorectal EMR. Differences in outcomes may benefit from increased assessment through well-designed comparative studies.

Key words: Colorectal; Colonic polyp; Endoscopic

mucosal resection; Endoscopic submucosal dissection; Colorectal cancer

Core tip: Endoscopic mucosal resection (EMR) is the conventional resection method of colorectal polyps. However certain lesions such as large sessile polyps can be challenging. Piecemeal resection has been shown to result in a high recurrence rate requiring further endoscopic sessions or surgery. Colorectal endoscopic submucosal dissection (ESD) is still at a relatively early stage, there are very few studies directly comparing the two modalities, few randomised controlled trials and fewer still reporting longer-term outcomes. This meta-analysis reports mid-term follow-up outcomes of colorectal ESD and EMR. ESD demonstrates higher *en-bloc* resection rates and lower mid-term recurrence rates compared to colorectal EMR albeit with higher complication rates.

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INTRODUCTION

Colorectal cancer is the fourth most common cancer in the world with an incidence of 9.7% and a 8.5% mortality rate[1]. The introduction of colorectal cancer screening programmes, particularly in the western world, and advancements in endoscopic imaging are likely to result in a greater number of early cancers and polyps detected.

The conventional endoscopic treatment of colorectal polyps is polypectomy or endoscopic mucosal resection (EMR) which is performed worldwide[2,3]. Performing EMR on lesions such as laterally spreading tumours or complex sessile polyps can be challenging and may require a number of endoscopic sessions or surgery resulting in extra cost, potential in-patient hospital stays, increased complication rates and stress to the patient[4,5]. Furthermore, piecemeal resection makes histopathological assessment of whether the procedure was curative or not difficult and has also been shown to result in a high recurrence rate[6-8].

As a result of the drive towards minimally invasive surgery, endoscopic submucosal dissection (ESD) has emerged as a viable endoscopic alternative for early colorectal cancers or polyps, which would otherwise have been treated surgically or endoscopically. The technique pioneered in Japan for early gastric cancer, has been used with great success particularly in East Asia[9-11] where it is now the standard of care. Given the success of the technique, the indications are now expanding and the technique is increasingly being used to treat colorectal lesions[5,12,13]. ESD has improved *en-bloc* resection rates for early gastric cancer compared to EMR[14-16]. However, the technique is also associated with long procedure times, greater complication rates as well as the need for a highly skilled endoscopist[5,17].

The uptake of colorectal ESD has been slow for a number of reasons. It is a more challenging technique than EMR and gastric ESD due to the long colonic lumen which has a thin luminal wall and comprises of flexures and folds resulting in an already technically demanding and complex technique becoming even more so.

Whether ESD outcomes, which have been so successful for early gastric cancer, can translate to colorectal lesions is not yet clear[18]. There are few studies directly comparing these techniques for colorectal lesions with insufficient information and varying short and mid-term outcomes[2,13,19-21].

The objective of this meta-analysis is to compare the outcomes of colorectal EMR and ESD from the literature to date. The efficacy of the techniques was determined by establishing the following primary outcomes: *En-bloc* resection rate, endoscopic completeness rate and recurrence rate. Secondary outcome measures include the complication rate including perforation, bleeding and surgery after EMR or ESD.

MATERIALS AND METHODS

Search strategy

An electronic search was conducted from four computerized databases, MEDLINE (1946 to end July 2014), EMBASE (1974 to end July 2014), Cochrane Central Register of Controlled Trials and systematic reviews (1991 to end July 2014), CINAHL (1937 to end July 2014) using the following search strategy: (Endoscopic mucosal resection OR EMR) AND (Endoscopic submucosal dissection OR ESD) AND (exp colonic polyps OR Colon) AND (exp endoscopic polypectomy OR polypectomy). Additional studies identified through relevant reviews, references cited by included papers and PubMed "related articles" feature were also examined in full text for potential inclusion (Figure 1).

Inclusion criteria

Studies which analysed the outcomes of colonic lesions (early cancers or polyps) removed by EMR and ESD were considered for inclusion in this meta-analysis.

The primary outcome measures were *en-bloc* resection rate, endoscopic clearance rate and lesion recurrence rate of the patients followed up. The secondary outcome was the complication rate (including bleeding, perforation and surgery post EMR or ESD rate). Both full articles and abstracts were included.

Exclusion criteria

Published abstracts or articles which did not contain a primary outcome variable were excluded. In addition, reviews, editorials, letters, opinions, comments, case reports and surveys were not included. Data which

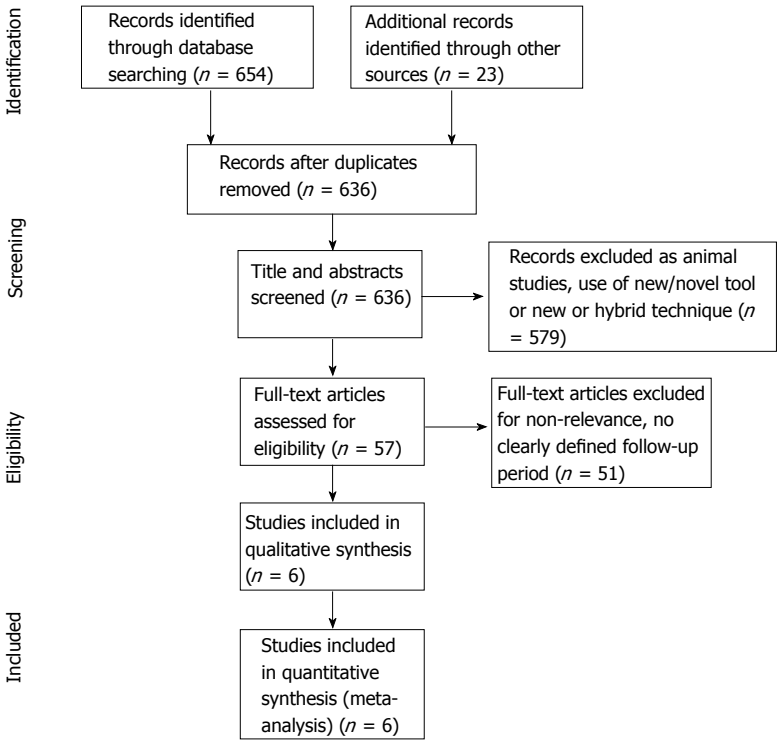

Figure 1 PRISMA flow diagram demonstrating search strategy.

Table 1 Study characteristics comparing outcomes of colorectal endoscopic mucosal resection *vs* endoscopic submucosal dissection

Ref.	Year	Study site	Publication type	Total sample size	EMR			ESD		
					Sample size	Male (%)	Age [mean ± SD (range)]	Sample size	Male (%)	Age [mean/median ± SD (range)]
Tajika *et al*[22]	2011	Japan	Full paper	189	104	61	59.9 ± 10.6	85	58	64.3 ± 9.2
Lee *et al*[23]	2012	South Korea	Full paper	454	140	64	63 (23-90)	314	55	61 (25-85)
Kobayashi *et al*[24]	2012	Japan	Full paper	84	56	68	65.9 ± 9.9	28	68	65.1 ± 9.7
Saito *et al*[25]	2010	Japan	Full paper	373	228	-	64 ± 4	145	-	64 ± 11
Kim *et al*[26]	2009	South Korea	Abstract	121	76	-	-	45	-	-
Tamegai *et al*[19]	2007	Japan	Full paper	103	32	-	-	71	54	63.4

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

had been published by the same research group or published by the same author were not included; only the most recent data which included the previously published data were included.

Papers which reported data for patients who were treated with ESD or EMR in different time periods or in different sites in the gastrointestinal tract were included if the colorectal data could be easily extracted. Animal studies and endoscopic removal of inflammatory polyps or neuroendocrine tumours were excluded. Studies which reported outcomes from snare-assisted, hybrid ESD, laparoscopic ESD or which used new endoscopic tools were excluded.

Data extraction

Eligible articles were reviewed independently by two investigators (NP and JA); data was extracted into a standardized data extraction form[19,22-26]. Discrepancies were resolved by a third investigator (JT) who made the final decision for eligibility and data extraction.

The following data were extracted where available: Year of publication, study location, patient demographics, operating time, lesion size, *en-bloc* resection rate, piecemeal resection rate, complete resection rate, length of follow-up, lesion recurrence and treatment, endoscopic completeness rate and complication rate (bleeding, perforation and surgery post ESD) (Tables 1-4).

En-bloc resection rate was defined as the removal of a lesion in one piece as observed endoscopically. Piecemeal resection was defined as the removal of a lesion in more than one piece as observed endoscopically. Once removed, resected specimens are evaluated histologically. Specimens with clear lateral and basal margins of tumour were defined as an R0 resection, incomplete (R1) resection was defined as a positive lateral or basal margin for tumour and Rx resection where the margins of the specimen could not be evaluated due to piecemeal resection or as a result of thermal injury during resection.

Table 2 Colorectal lesion characteristics

Ref.	Lesion size [mean ± SD (range) mm]		Operating time [mean or median ± SD (range) min]		Lesion location (EMR: ESD cases)			Lesion type (EMR:ESD cases)						
	EMR	ESD	EMR	ESD	Left colon	Right colon	Rectum	Sessile	Depressed	Protruding	LST-G	LST-NG	LST-F	Recurrence
Tajika *et al*[22]	25.5 ± 6.8 (20-55)	31.6 ± 9 (20-54)	29.4 ± 26.1 (3-115)	87.2 ± 49.7 (19-256)	41:13	35:41	28:31		0:1	68:10	28:33	7:38		1:3
Lee *et al*[23]	21.7 ± 3.5 (20-40)	28.9 ± 12.7 (20-145)	-	54.73 ± 40.9 (6-321)	41:82	82:172	0.75	36:73			49:129	55:112		
Kobayashi *et al*[24]	25 ± 9	27.1 ± 10.1	11 (2-280)	140 (45-400)	26:14	15:6	15:8			12:0	22:6	22:20		0:6
Saito *et al*[25]	28 ± 8 (20-95)	37 ± 14 (20-140)	29 ± 25 (3-120)	108 ± 7 (15-360)	52:28	89:44	110:73	80:5	0:2		114:62	34:71		
Kim *et al*[26]	-	-	-	-	-	-	-				28:48	6:16	22:2	
Tamegai *et al*[19]	28.7 (20-60)	32.1 (13-75)	-	61.1 (7-164)	-:28	-:26	-:17		0:2	12:19				

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST-G: Laterally spreading tumour granular type; LST-NG: Laterally spreading tumour nodular granular type; LST-F: Laterally spreading tumour flat type.

Table 3 The outcomes of endoscopic mucosal resection and endoscopic submucosal dissection of colorectal lesions

Ref.	*En-bloc* resection rate (%)		Piecemeal resection rate (%)		R0 lesion margins (%)		Endoscopic completeness rate (%)		Bleeding rate EMR: ESD (%)	Perforation rate EMR: ESD (%)	Total complication rate (%)	Surgery post EMR/ESD (EMR:ESD cases)	
	EMR	ESD	EMR	ESD	EMR	ESD	EMR	ESD				Due to perfor-ation	Due to deep invasion
Tajika *et al*[22]	48.1	83.5	52.9	16.5	39.4	83.5	97	98.8	2.9:2.4	0:5.9	2.9:8.2	0:3	0
Lee *et al*[23]	42.9	92.7	57.1	7.3	32.9	87.6	99.1	90.8	0:0.6	0:8	5.7:11.5	0:2	9:26
Kobayashi *et al*[24]	37.5	92.9	62.5	7.1	-	-	98.2	100	1.8:7.1	0:10.7	1.8:17.9	0	0
Saito *et al*[25]	33	84	67	16	-	-	98.7	100	3.1:1.4	1.3:6.2	4.4:7.6	0	0
Kim *et al*[26]	72.4	80	27.6	20	-	-	100	100	-	-	3.9:6.7	-	-
Tamegai *et al*[19]	0	98.6	100	1.4	-	95.6	100	90.1	-:0	-:1.4	-:1.4	-	-:7

NB total complication rate includes coagulation syndrome. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 4 Recurrent lesion characteristics

Ref.	Follow-up time (mean or median ± SD, range) (mo)		Recurrence rate (%)		Piecemeal resection rate of recurrent lesions (%)		Recurrent lesion histology (EMR: ESD cases)				Treatment of recurrent lesion (EMR:ESD cases)		
	EMR	ESD	EMR	ESD	EMR	ESD	Adenoma	Non-inv cancer	Sm1	Invasive cancer	APC	EMR	Surgery
Tajika *et al*[22]	53.8 ± 44.6 (3-191	14.3 ± 13.4 (3-53)	15.4	1.2	94	100	13/16:0	3/16:0	0:1/1	0:0	7/16:0	8/16:0	1/16:1/1
Lee *et al*[23]	26 (IQ range 13-41)	17 (IQ range 10-23)	25.7	0.8	90	50	-:2/2 (serrated)	-	-	-	0:0	28/29:2/2	1/29:0
Kobayashi *et al*[24]	38 (2.8-112.5)	19.9 (6.4-43.9)	21.4	0	92	n/a	8/12:0	3/12:0	0	1/12:0	0:0	11/12:0	1/12:0
Saito *et al*[25]	26 ± 17 (6-68)	20 ± 13 (6-61)	14	2	94	100	-:3/3	-	-	2/33:0	0:0	30/33: 3/33	3/33:0
Kim *et al*[26]	12 (6-12)	12 (6-12)	11.8	4.8	-	0	-	1/1:0	0	0:0	-	-	-
Tamegai *et al*[19]	19.2 (3-34)	12.2 (3-34)	6.3	0	100	-	-	-	-	-	-:0	2/2:0	0:0

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; APC: Argon photocoagulation.

Endoscopic clearance rates were defined as complete endoscopic removal of a lesion *en-bloc* or piecemeal and at one or more procedures.

Risk of bias assessment

The studies were assessed using the risk of bias tool from the Cochrane Collaboration[27] (Figure 2). The risk of

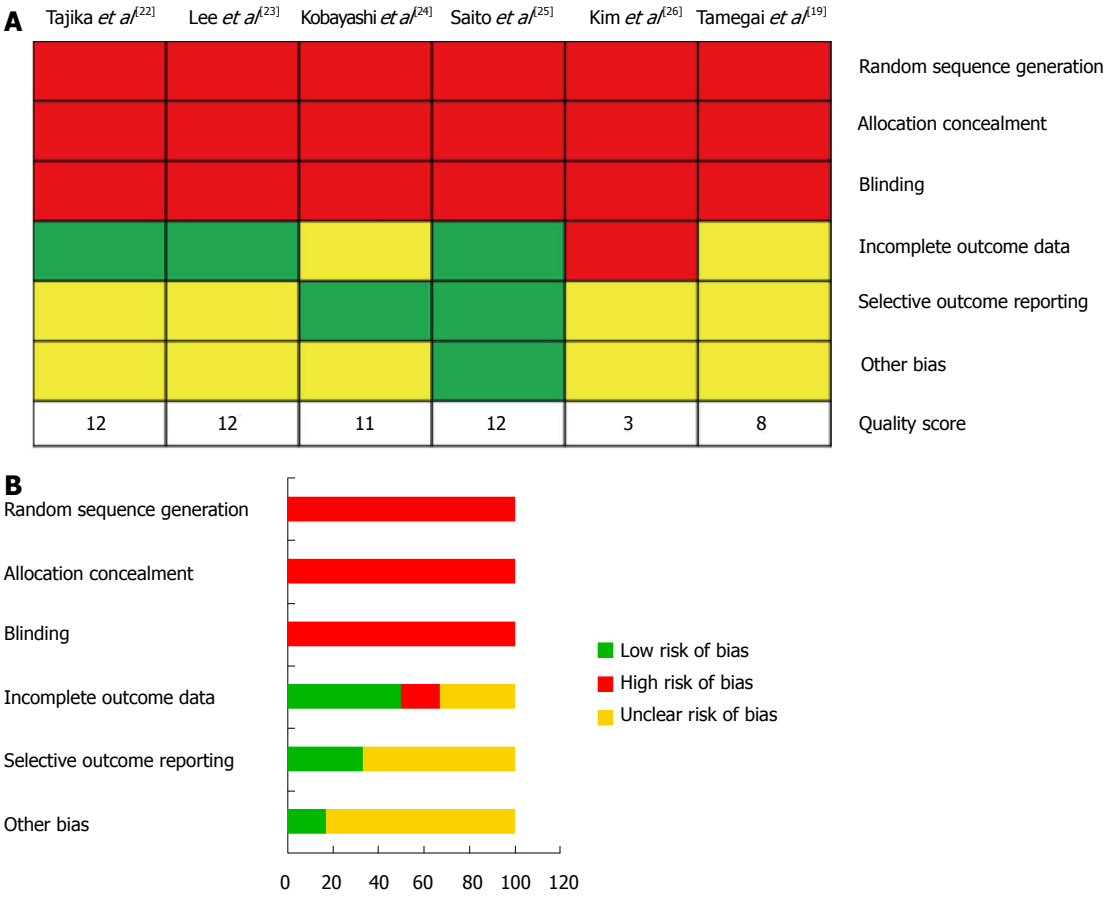

Figure 2 Risk of bias graph (A) and risk of bias summary (judgments of each risk criteria presented as percentages across all included studies) and quality score results (B).

bias assessment domains examined were: (1) adequate sequence generation, determining if the allocation sequence generated by a computer or random numbers was adequate; (2) allocation concealment, determining if the participants and investigators enrolling the patients could foresee the study treatment arms during allocation; (3) blinding, which assessed if the study personnel, participants and assessors had knowledge of the allocation interventions during the study; (4) data reporting, determining if incomplete outcome data were adequately addressed; (5) selective outcome reporting, which is if the study protocols, primary outcomes and analysis methods are reported; and (6) other potential risks to study validity such as a potential source of bias related to the study design, or that the study was prematurely stopped due to a data-dependent process or fraudulent claims.

The quality of included studies was assessed using a modified Newcastle-Ottawa scale (Table 5). The quality domains examined were (1) patient selection; (2) intergroup comparability; and (3) outcome assessment using a star based system (maximum 3, 10 and 2 stars, respectively, total /15). The scoring was independently assessed by two authors (Patel N and Alexander J), with 100% inter-rater agreement (Figure 2).

Statistical analysis

Proportion difference between EMR and ESD outcomes and calculated risk differences were calculated and pooled through DerSimonian and Laird random-effects modelling[27]. This considered both between-study and within-study variances which contributed to study weighting. Pooled values and 95%CIs were computed and represented on funnel plots. Statistical heterogeneity was determined by the I^2 statistic; where < 30% is low, 30%-60% is moderate and > 60% is high. Analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, United States).

RESULTS

The literature search identified 677 potential studies (Figure 1). The majority of these were excluded as they reported outcomes from animal studies, the use of new tools or a hybrid technique. Of the 57 studies that were assessed in full text for eligibility, 51 were excluded for the following reasons: No data on all primary outcome measures, no clearly defined follow up period, repeated published data and upper gastrointestinal endoscopic therapy. The final analysis included six studies published from 2007 to 2012 reporting 1324 lesions subjected to analysis, of which 688 were in the ESD group and 636 in the EMR group. Adequate demographic data was reported in three studies[22-24], 59% of patients were men and 41% were women. The mean age was 62.5 years in the EMR group, and 61.9 years in the ESD

Table 5 Criteria for modified newcastle ottawa scoring system

Quality Checklist	
Selection	
1	Assignment for treatment-any criteria reported (if yes, 1-star)?
2	How representative was the reference group (EMR group) in comparison to the general population for colorectal lesions? (If yes, 1-star, no stars if the patients were selected or selection of group was not described)
3	How representative was the treatment group (ESD group) in comparison to the general population for colorectal lesions? (If drawn from the same community as the reference group, 1-star, no stars if drawn from a different source or selection of group was not described)
Comparability	
Comparability variables	(1) Age; (2) gender; (3) lesion size; (4) LST; (5) lesion location; (6) LGD; (7) HGD; (8) submucosal tumor; (9)non-invasive cancer; (10) cancer
4	Groups comparable for 1, 2, 3, 4, 5 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups differed)
5	Groups comparable for 6, 7, 8, 9, 10 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups differed)
Outcome assessment	
6	Clearly defined outcome of interest (if yes, 1-star)
7	Follow-up (1-star if described)

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST: Lateral spreading tumor; LGD: Low grade dysplasia; HGD: High grade dysplasia.

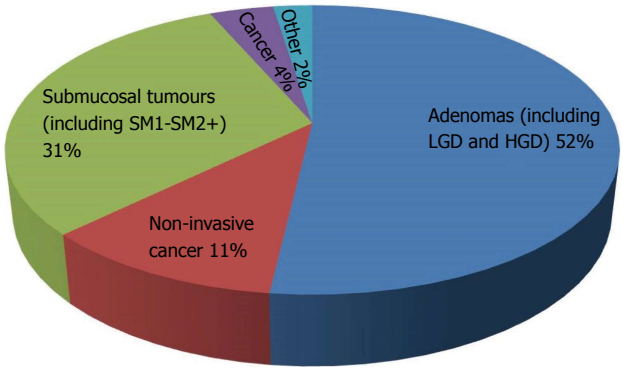

Figure 3 Colorectal lesion histopathology. LGD: Low grade dysplasia; HGD: High grade dysplasia; SM1: Submucosal tumour < 1000 μm invasion depth; SM2: Submucosal tumour > 1000 μm invasion depth.

group (Table 1).

Mean procedure times were reported in four studies[19,22,23,25] (Table 2). The overall mean time was 29 min (range 2-280) for EMR[22,25] and 73 min (range 6-400) for ESD[19,22,23,25]. The mean follow up period was 29.7 mo in the EMR group and 15.9 in the ESD group, as reported in 4 studies[19,22,25,26] (Table 4).

Five studies reported data on the size of lesions[19,22-25] (Table 2). The mean size of lesion was 25.7 mm (range 20-95 mm) in the EMR group and 31.4 mm (range 13-145 mm) in the ESD group. The location of lesions was reported in three studies[22-24] shown in Table 2. In the EMR group, 44% lesions were in the right colon, 36% lesions were in the left colon and 20% were in the rectum. In the ESD group, 51% lesions were in the right colon, 26% were in the left colon and 23% in the rectum. Data on lesion type was available for 93% of all lesion outcomes reported (Table 2). The majority of procedures were carried out on lateral spreading tumour (LST) (365/574 treated by EMR and 535/656 by ESD). In the EMR group, 66% were the granular type (LST-G) and 23% were non-granular (LST-NG). In the ESD group, 52% were LST-G and 48% LST-NG. EMR was performed in a greater number of sessile lesions (20% EMR, 12% ESD) and protruding lesions (16% EMR, 4% ESD). ESD was performed in a greater number of patients with depressed or recurrent lesions (0.2% EMR, 2% ESD).

Histologically, 52% of lesions were adenomas (including low grade and high grade dysplasia). Eleven percent of lesions were described as non-invasive mucosal cancers and 4% as cancers. Submucosal tumours (SM1 and SM2+) made up 31% of the lesions resected (Figure 3).

Outcomes

The *en-bloc* resection rate was reported in all studies (Table 3). This demonstrated a 50% higher *en-bloc* resection rate in the ESD than the EMR group (95%CI: 0.17-0.83, $P < 0.0001$, $I^2 = 99.7$ %) (Figure 4).

The piecemeal resection rate was also reported in all six studies (Table 3). The rate of piecemeal resection was 48% higher in the EMR group than in the ESD group (95%CI: -0.70-0.26, $P < 0.0001$, $I^2 = 96.7$%) (Figure 5).

The endoscopic clearance rate was reported in all studies (Table 3). This demonstrated a marginal but significant, 2% higher rate in the ESD group compared to the EMR group (95%CI: -0.06-0.02, $P < 0.0001$, $I^2 = 92.5$%) (Figure 6).

The R0 rates were reported in both groups in two studies[22,23] and only the ESD group from Tamegai *et al*[19]. The average R0 rate for the EMR group was 36.2% and 88.9% in the ESD group.

Complications

The total reported complication rate, including perforation, bleeding and coagulation syndrome, was 3.9% in the EMR group and 9.2% in the ESD group. The perforation rate for both EMR and ESD was reported in four of the six studies (Tamegai *et al*[19] only reported perforation rate for ESD). The perforation rate was 7% higher in the ESD

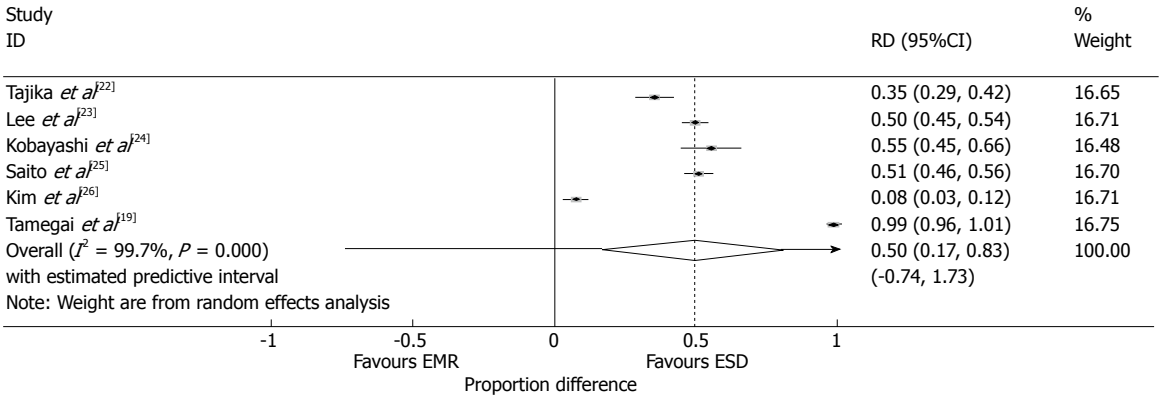

Figure 4 ***En-bloc*** **resection proportion difference endoscopic mucosal resection *vs* endoscopic submucosal dissection.** EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

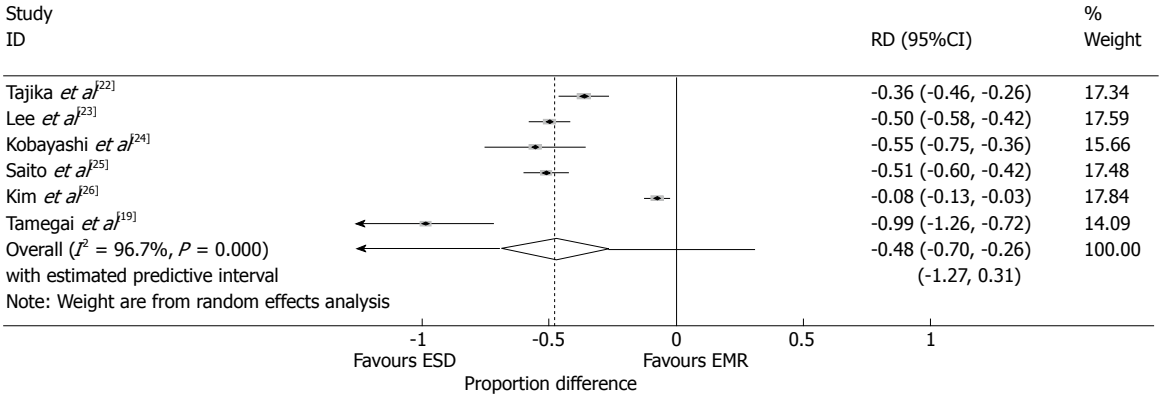

Figure 5 Piecemeal resection proportion difference endoscopic mucosal resection *vs* endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

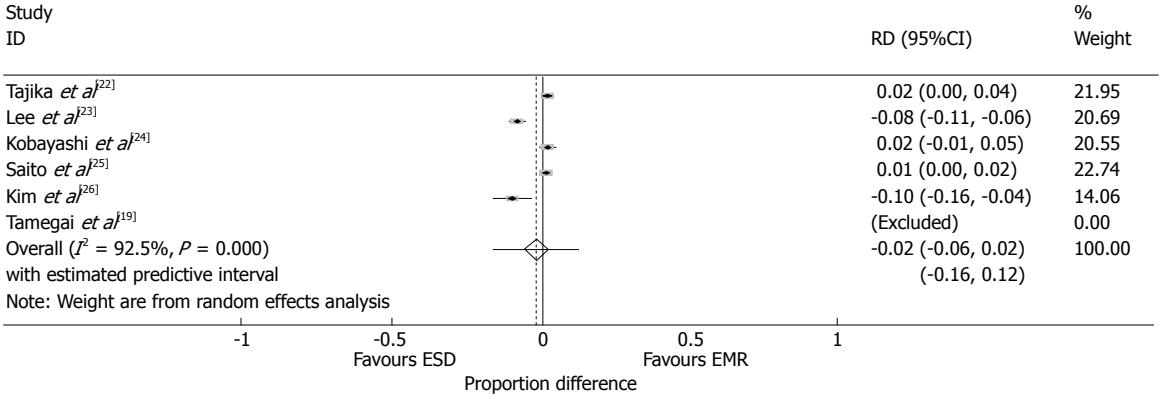

Figure 6 Endoscopic completeness rates proportion difference endoscopic mucosal resection *vs* endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

group than the EMR group (95%CI: 0.05-0.09, $P > 0.05$, $I^2 = 41.1\%$) (Figure 7). Five patients required surgery due to perforation in the ESD group, compared to none in the EMR group (Table 3).

Recurrence rate

The recurrence rate was reported in all studies (Table 4). In cases that were followed up, the rate of recurrence was 50% higher in the EMR group than in the ESD group (95%CI: 0.20-0.79, $P < 0.001$, $I^2 = 99.5\%$) (Figure 8). The resected margins were reported in Tajika *et al*[22]. In the EMR group 7/16 cases had R1 margins and 9/16 Rx margins. In the ESD group, 41/56 cases were R0, 6/56 R1 and 9/56 cases Rx. All studies except Kim *et al*[26] reported the piecemeal rate in the recurrence groups. 92% (85/92) of cases in the EMR group and 71% (5/7) of cases in the ESD group had been removed by piecemeal. The recurrent lesions in

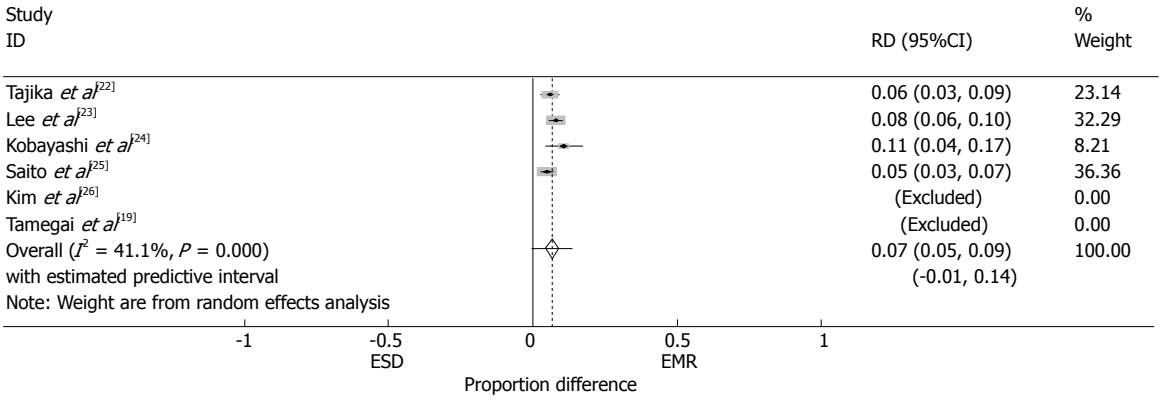

Figure 7 Perforation proportion difference endoscopic mucosal resection *vs* endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

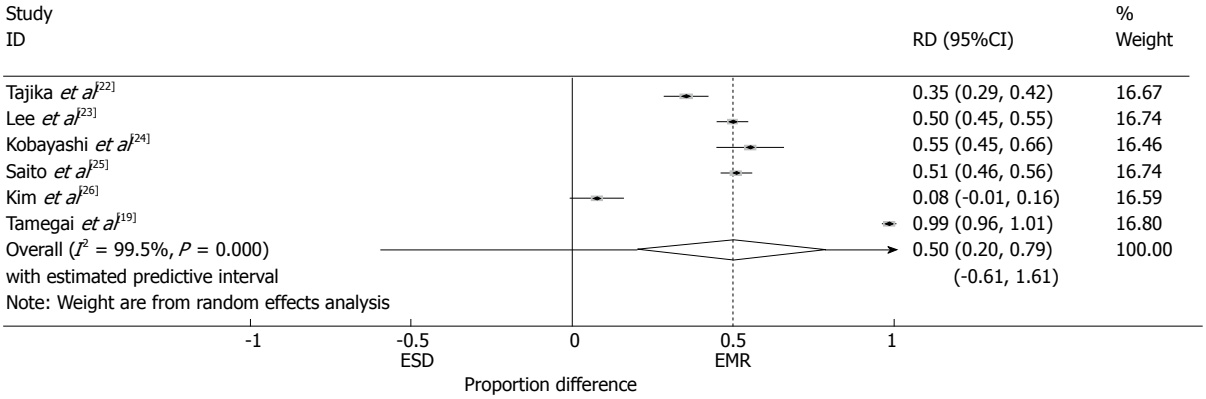

Figure 8 Recurrence proportion difference endoscopic mucosal resection *vs* endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 6 Sub-group analysis of the four highest quality studies[22-25]

	I^2 (%)	*P* value	95%CI	Effect size
En-bloc resection rate	82.3	< 0.0001	0.14-0.81	0.476
Piecemeal resection rate	51.7	0.102	-0.76-0.19	-0.472
Endoscopic completeness rate	93.1	< 0.0001	0.19-0.17	-0.008
Recurrence rate	82.1	< 0.0001	0.13-0.82	0.476

both groups were mainly adenomas (21/32 recurrent EMR cases and 5/6 ESD cases (data not available from Kim *et al*[26] in the ESD group). There were three invasive cancers reported as recurrent lesions in the EMR group and none in the ESD group. Seventy nine of the recurrent EMR cases were successfully treated with repeat EMR procedures, seven cases with argon photocoagulation and six required surgery (a portion of this group had multiple previous attempts at EMR before technical difficulties or invasive carcinoma were found at a later date) (data not available from Kim *et al*[26]). In the ESD group, 5 recurrent cases were successfully treated with EMR and one with surgery[22] (Table 4).

Risk of bias and quality scoring

All of the included trials had a high risk or unclear risk of bias in one or more of the assessed domains (Figure 2). Random sequence generation, allocation concealment and blinding were the main potential risks of bias in studies included in this meta-analysis. The overall quality scores are shown in Figure 2. Four studies received score of $\geqslant$ 10 and were hence deemed to be of relative high quality. These studies were analysed as a sub-group to determine the source of heterogeneity (Table 6). There was no substantial change in heterogeneity when *en-bloc* resection rate, endoscopic completeness rate and recurrence rates were re-analysed. Piecemeal resection rates however demonstrated a reduction from significant to moderate heterogeneity though effect sizes remained similar throughout. All studies adequately matched both EMR and ESD groups for comparability and outcome assessment.

DISCUSSION

This is one of the first meta-analyses comparing the outcomes of colorectal ESD and EMR. The pooled outcome results of this meta-analysis (from non-comparative studies) suggest that there may be a perceptible difference in the clinical outcomes colorectal of ESD and EMR. The results for ESD demonstrated higher *en-bloc* resection rates, endoscopic clearance rates and lower recurrence rates, albeit with higher pooled outcome complication

rates. However, any inferences regarding clinical superiority should be taken with caution, as these results do not derive from comparative studies and demonstrate high heterogeneity throughout.

Although EMR is an established technique, it is usually performed for smaller lesions or larger lesions in piecemeal (associated with higher recurrence rates). Piecemeal resection involving multiple smaller resections often makes the endoscopic field difficult to detect residual tissue due to electrocautery burns, blood and local trauma. Further therapeutic procedures may therefore be required with cost, time and increased complication rate implications. In comparison, creating a mucosal incision around the lesion during ESD means that the endoscopic resection margins have already been delineated minimising disruption of the endoscopic field during submucosal dissection.

ESD appears advantageous as it allows accurate histopathological assessment of the resected lesion and resected margins, associated with fewer reported recurrences or residual disease. However, colorectal ESD is technically complex requiring more highly skilled endoscopists compared to upper gastrointestinal ESD. Compared to EMR, the procedure times are longer, more demanding and have higher complication rates.

There are endoscopic tools which have been developed or are in development designed to facilitate ESD and further improve clinical effectiveness, long-term outcomes and safety. For example, hydrodissection in the submucosal plane can be performed using the HybridKnife (ERBE)[28] and a hybrid ESD approach using a snare has also been introduced.

ESD has been shown to result in significantly lower recurrence rates compared to EMR. This may result from greater *en-bloc* resection rates, lower piecemeal rates and, in the studies that reported the resected margins, a higher R0 rate. However, ESD is more time consuming and associated with significantly greater complication rates. Safety of the technique is an important consideration, particularly if the uptake of ESD is to increase. There are technical difficulties of performing ESD in the colonic environment which is thin-walled containing flexures and folds. However, it will be interesting to monitor the uptake and outcomes in countries other than East Asia such as the Western world where, although the incidence of colorectal cancer is higher, upper gastrointestinal ESD is an infrequent occurrence. In these countries the learning curve is likely to be greater as a result of difficulties with training opportunities resulting from a lack of clinical cases, experience and skilled tutors.

Trans-anal endomicroscopy allows full-thickness resection of rectal lesions with accurate staging albeit with a higher complication rate compared to endoscopic therapy. In addition, conventional rectal surgery is more invasive with the risk of stoma formation and problems with incontinence resulting in a drive for a favourable minimally invasive endoscopic approach. However, differences between rectal and colonic lesion endotherapy outcomes have been reported[29]. This is multifactorial with anatomical and vascular differences between the two sites. The rectum is the first place to start training endoscopists in ESD because it is easily accessible compared to other parts of the colon[30]. Furthermore, rectal insufflation creates a neat and stable workspace to perform ESD compared to a mobile, narrow colon with folds or flexures to consider. Significantly higher recurrence rates have been reported in patients with high-risk submucosal rectal cancers treated with endoscopic therapy compared to colonic lesions[29]. Further analysis of endoscopic therapy comparing these two lesion locations is required to determine whether or not definite surgical measures with lymph node dissection rather than ESD for these higher risk patients is a better longer-term treatment plan. To improve the quality of analysis of colorectal ESD outcomes, prospective randomised controlled trials with appropriate follow-up periods which also accommodate for learning curve effects and include quality of life data are required to validate the technique in the lower gastrointestinal tract.

Limitations

There are a number of limitations to this analysis which derive from significant clinical and statistical heterogeneity throughout. The significant statistical heterogeneity demonstrated suggests there is a risk the included studies were clinically heterogenous. This may result in the effect size difference being a secondary finding or a high risk for bias finding. The four high quality studies were also studied as a subgroup to determine if the heterogeneity decreases[22-25]. This only decreased from significant to moderate for piecemeal resection and effect sizes remained similar throughout. The quality scores of many of the included studies was moderate, there are few studies directly comparing the outcomes of colorectal ESD and EMR and no randomised controlled trials in the literature to date. The eligibility criteria are often unclear for both techniques, lesions had differing characteristics and size and all of the included studies were retrospective case-control studies or observational studies.

In addition, all the included studies originated from East Asia (Japan and South Korea) where there are a larger number of endoscopists familiar with the technique and hence this may cause bias. In a number of studies the time periods during which EMR and ESD were carried out were different reflecting a change in practice with the introduction of ESD[19,22,23]. The outcomes of the studies may have hence been subject to bias with improvements in endoscopy technique and introduction of ESD tools and devices to facilitate the procedure reflected in the significant heterogeneity of the resulting outcomes. The effect size may also have been affected by the learning curve effect. Five out of the six studies scored poorly for the quality of patient selection, particularly how representative the groups were. The selection of the groups was not described

adequately in these studies and may be reflected by the significant heterogeneity of the results.

Follow-up periods also differed in these studies and as a result lead-time and selection biases may have also occurred. Follow-up in some studies was difficult as the procedures were often carried out at tertiary referral centres with follow-up at local hospitals where the outcome data were not reported[24,25].

In conclusion, Whilst ESD for early non-metastatic gastric cancer is now the treatment of choice in East Asia and is gaining popularity worldwide, colorectal ESD is still at a relatively early stage. The adoption of the technique in the West is particularly important given the significantly higher incidence and is another step towards the scarless surgery goal. The colonic environment is more challenging than the upper gastrointestinal tract and there is a learning curve to the technique. However, *en-bloc* resection has significantly more favourable mid-term outcomes compared to EMR. This is in addition to the benefits of not performing a surgical procedure in terms of recovery, cost and complications.

This meta-analysis reports on mid-term follow-up outcomes. In order to better identify the differences in outcome between these two modalities, case-matched prospective and randomised studies should be carried out with protracted follow-up periods to ascertain longer-term outcomes. The trade-off between safety and risk of perforation also needs to be established, patient selection and analysis of ESD and EMR colorectal registry data will be useful to establish this through more robust data in the future.

ACKNOWLEDGMENTS

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COMMENTS

Background

Minimally invasive endosurgical techniques such as endoscopic submucosal dissection (ESD) are gaining popularity worldwide as an alternative to conventional surgery. Whilst ESD for early non-metastatic gastric cancer is the treatment modality of choice in East Asia, the uptake of the technique in the Western world has been slow. This is in part due to the appropriate case load and also due to the high complexity of the technique. Colorectal cancer and polyps are highly prevalent in the Western world and hence endoscopic submucosal dissection should be explored and compared to current endoscopic therapy.

Research frontiers

A meta-analysis was used to evaluate the mid-term outcomes of colorectal ESD and endoscopic mucosal resection (EMR).

Innovations and breakthroughs

This is one of the first detailed meta-analysis evaluating immediate and mid-term outcomes for colorectal ESD and EMR. Most of the literature to date report immediate outcomes after endoscopic therapy, there is no longer-term outcome data and little mid-term outcome data reported.

Applications

This meta-analysis showed that colorectal ESD demonstrates higher *en-bloc* resection rates and lower recurrence rates compared to colorectal EMR. Although the complication rates are higher with a significantly increased perforation rate, ESD obviates the need for surgery and reduces the need for further endoscopic procedures. Differences in outcomes may benefit from increased assessment through well-designed comparative studies.

Peer-review

This is a good meta-analysis, suitable for publication. This meta-analyses study reports the comparison between EMR and ESD for colorectal lesions. Although this kind of meta-analyses is not the first report, this is still useful to compare both methods for colorectal tumours.

REFERENCES

1 **Ferlay J**, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: URL: http://globocan.iarc.fr

2 **Kudo S**. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy* 1993; **25**: 455-461 [PMID: 8261988 DOI: 10.1055/s-2007-1010367]

3 **Tanaka S**, Oka S, Chayama K, Kawashima K. Knack and practical technique of colonoscopic treatment focused on endoscopic mucosal resection using snare. *Dig Endosc* 2009; **21** Suppl 1: S38-S42 [PMID: 19691731 DOI: 10.1111/j.1443-1661.2009.00857.x]

4 **Hurlstone DP**, Cross SS, Brown S, Sanders DS, Lobo AJ. A prospective evaluation of high-magnification chromoscopic colonoscopy in predicting completeness of EMR. *Gastrointest Endosc* 2004; **59**: 642-650 [PMID: 15114306 DOI: 10.1016/S0016-5107(04)00156-7]

5 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973 [PMID: 17524403 DOI: 10.1016/j.gie.2007.02.053]

6 **Conio M**, Repici A, Demarquay JF, Blanchi S, Dumas R, Filiberti R. EMR of large sessile colorectal polyps. *Gastrointest Endosc* 2004; **60**: 234-241 [PMID: 15278051 DOI: 10.1016/S0016-5107(04)01567-6]

7 **Fukami N**, Lee JH. Endoscopic treatment of large sessile and flat colorectal lesions. *Curr Opin Gastroenterol* 2006; **22**: 54-59 [PMID: 16319677 DOI: 10.1097/01.mog.0000198075.59910.1f]

8 **Min BH**, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim KM, Park CK, Rhee JC. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). *Dig Liver Dis* 2009; **41**: 201-209 [PMID: 18571998 DOI: 10.1016/j.dld.2008.05.006]

9 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]

10 **Ono H**. Endoscopic submucosal dissection for early gastric cancer. *Chin J Dig Dis* 2005; **6**: 119-121 [PMID: 16045601 DOI: 10.1111/j.1443-9573.2005.00206.x]

11 **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin Gastroenterol Hepatol* 2007; **5**: 678-683; quiz 645 [PMID: 17466600 DOI: 10.1016/j.cgh.2007.01.006]

12 **Yamamoto H**, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K. Successful

en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690-694 [PMID: 12929067 DOI: 10.1055/s-2003-41516]

13 **Sano Y**, Machida H, Fu KI, Ito H, Fuji T. Endoscopic mucosal resection and submucosal dissection method for large colorectal tumours. *Dig Endosc* 2004; **16**: S93- S96 [DOI: 10.1111/j.1443-1661.2004.00375.x]

14 **Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 2962-2967 [PMID: 18494043 DOI: 10.3748/wjg.14.2962]

15 **Yahagi N**, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, Iguchi M, Enomoto S, Ichinose M, Niwa H, Omata M. Endoscopic submucosal dissection for early gastric cancer using tip of an electrosurgical snare (thin type). *Dig Endosc* 2004; **16**: 34-38 [DOI: 10.1111/j.1443-1661.2004.00313.x]

16 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]

17 **Yoshida N**, Wakabayashi N, Kanemasa K, Sumida Y, Hasegawa D, Inoue K, Morimoto Y, Kashiwa A, Konishi H, Yagi N, Naito Y, Yanagisawa A, Yoshikawa T. Endoscopic submucosal dissection for colorectal tumors: technical difficulties and rate of perforation. *Endoscopy* 2009; **41**: 758-761 [PMID: 19746316 DOI: 10.1055/s-0029-1215028]

18 **Toyanaga T**, Man-I M, Ivanov D, Sanuki T, Morita Y, Kutsumi H, Inokuchi H, Azuma T. The results and limitations of endoscopic submucosal dissection for colorectal tumors. *Acta Chir Iugosl* 2008; **55**: 17-23 [PMID: 19069688 DOI: 10.2298/ACI0803017T]

19 **Tamegai Y**, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E, Liu Y, Uemura N, Saito K. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418-422 [PMID: 17516348 DOI: 10.1055/s-2007-966427]

20 **Uraoka T**, Kato J, Ishikawa S, Harada K, Kuriyama M, Takemoto K, Kawahara Y, Saito Y, Okada H. Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). *Gastrointest Endosc* 2007; **66**: 836-839 [PMID: 17905031 DOI: 10.1016/j.gie.2007.04.028]

21 **Saito Y**, Mashimo Y, Kikuchi T, Ikehara H, Uraoka T, Matsuda T, Fukuzawa M, Saito D. Endoscopic Submucosal Dissection Resulted in Higher En-Bloc Resection Rates and Reduced Lower Recurrence for LSTS 20 mm Compared to Conventional EMR. *Gastrointest Endosc* 2007; **65**: AB273 [DOI: 10.1016/j.gie.2007.03.657]

22 **Tajika M**, Niwa Y, Bhatia V, Kondo S, Tanaka T, Mizuno N, Hara K, Hijioka S, Imaoka H, Ogura T, Haba S, Yamao K. Comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors. *Eur J Gastroenterol Hepatol* 2011; **23**: 1042-1049 [PMID: 21869682 DOI: 10.1097/MEG.0b013e32834aa47b]

23 **Lee EJ**, Lee JB, Lee SH, Youk EG. Endoscopic treatment of large colorectal tumors: comparison of endoscopic mucosal resection, endoscopic mucosal resection-precutting, and endoscopic submucosal dissection. *Surg Endosc* 2012; **26**: 2220-2230 [PMID: 22278105 DOI: 10.1007/s00464-012-2164-0]

24 **Kobayashi N**, Yoshitake N, Hirahara Y, Konishi J, Saito Y, Matsuda T, Ishikawa T, Sekiguchi R, Fujimori T. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012; **27**: 728-733 [PMID: 22004124 DOI: 10.1111/j.1440-1746.2011.06942.x]

25 **Saito Y**, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* 2010; **24**: 343-352 [PMID: 19517168 DOI: 10.1007/s00464-009-0562-8]

26 **Kim DU**, Song GA, Lee SM, Kim TO, Kim GH, Heo J. Endoscopic Mucosal Resection Versus Endoscopic Submucosal Dissection According to the Sizes and the Subtypes of Laterally Spreading Tumors. *Gastrointest Endosc* 2009; **69**: AB282 [DOI: 10.1016/j.gie.2009.03.764]

27 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

28 **Schumacher B**, Charton JP, Nordmann T, Vieth M, Enderle M, Neuhaus H. Endoscopic submucosal dissection of early gastric neoplasia with a water jet-assisted knife: a Western, single-center experience. *Gastrointest Endosc* 2012; **75**: 1166-1174 [PMID: 22482915 DOI: 10.1016/j.gie.2012.02.027]

29 **Ikematsu H**, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Murakami Y, Fujimori T, Kaneko K, Saito Y. Long-term outcomes after resection for submucosal invasive colorectal cancers. *Gastroenterology* 2013; **144**: 551-559; quiz e14 [PMID: 23232297 DOI: 10.1053/j.gastro.2012.12.003]

30 **Iacopini F**, Bella A, Costamagna G, Gotoda T, Saito Y, Elisei W, Grossi C, Rigato P, Scozzarro A. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest Endosc* 2012; **76**: 1188-1196 [PMID: 23062760 DOI: 10.1016/j.gie.2012.08.024]

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Computed tomography fluoroscopy guided percutaneous lung biopsy for ground-glass opacity pulmonary lesions: A meta-analysis

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Abstract

AIM: To obtain the diagnostic performance of percutaneous transthoracic needle biopsy (PTNB) under Computed tomography (CT) fluoroscopy guidance for lung ground-glass opacity (GGO).

METHODS: We searched for English- and Chinese-language studies in PubMed, EMBASE, EBSCO, OVID, and CNKI (China National Knowledge Infrastructure) database. Data were calculated with Meta-Disc version 1.4 and Rev Man version 5.2 software. From the pooled data, we calculated sensitivity (Sen), specificity (Spe), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR). Summary receiver operating characteristic (SROC) curves were constructed and incidence of complications was recorded.

RESULTS: Four documents included in this present meta-analysis met the criteria for analysis. The pooled Sen, Spe, +LR, -LR and DOR with 95%CI were 0.91 (0.86-0.95), 1.0 (0.91-1.0), 18.64 (4.83-71.93), 0.11 (0.05-0.26) and 153.17 (30.78-762.33), respectively. The area under the SROC curve was 0.98. The incidence of pneumothorax and hemoptysis was 17.86%-51.80% and 10.50%-19.40%, respectively.

CONCLUSION: CT fluoroscopy-guided PTNB, which has an acceptable incidence of complications, can be used

as a primary examination method for lung GGO, with moderate sensitivity and specificity.

Key words: Lung biopsy; Meta-analysis; Ground-glass opacity; Computed tomography fluoroscopy

Core tip: There is no consensus in the literature about the diagnostic performance of percutaneous transthoracic needle biopsy (PTNB) under Computed tomography (CT) fluoroscopy guidance for lung ground-glass opacity (GGO). We performed a meta-analysis to obtain the diagnostic performance of CT fluoroscopy-guided PTNB of lung GGO in terms of pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio and incidence of complications. We also generated a summary receiver operating characteristic curve as a way of summarizing the global test performance of CT fluoroscopy-guided PTNB.

Yan GW, Yan GW, Sun QQ, Niu XK, Li B, Bhetuwal A, Xu XX, Du Y, Yang HF. Computed tomography fluoroscopy guided percutaneous lung biopsy for ground-glass opacity pulmonary lesions: A meta-analysis. *World J Meta-Anal* 2016; 4(2): 55-62 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i2/55.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i2.55

INTRODUCTION

Ground-glass opacity (GGO) in lung parenchyma is a image manifestation on thin-section Computed tomography (CT) that is defined as "hazy increased attenuation of the lung with preservation of bronchial and vascular margins"[1]. As prevalence of lung cancer screening with low-dose CT rises, so has the detection of pulmonary lesions that manifest as GGO nodules[2,3]. Since, GGO, not being a specific imaging finding, many differential diagnoses such as bronchoalveolar carcinoma, adenocarcinoma, atypical adenomatous hyperplasia, focal fibrosis and inflammatory diseases must be taken into consideration[4,5]. As a result, the importance of diagnosing lung GGO cannot be ignored once observation, clinical follow-up or chemotherapeutic therapy has ruled out the benign or inflammatory nature of the lesion. However, controversy does exist on whether PTNB should be attempted for the persistent presence of lung GGO or not.

Recent efforts[6-9] utilizing PTNB under the guidance of CT fluoroscopy have been attempted to increase the diagnostic accuracy of lung GGO but contain only few enrolled subjects. The objective of this article was to obtain the diagnostic performance of CT fluoroscopy guided PTNB for lung GGO with a meta-analysis, which, as far as the authors' understanding, has not been reported previously.

#1 ("CT" or "computed tomography" or "CT fluoroscopy" or "CTF") [Title/Abstract]
#2 ("ground-glass opacity" or "GGO") [Title/Abstract]
#3 ("lung" or "pulmonary") [Title/Abstract]
#4 #1 and #2 and #3

Figure 1 Search strategy for PubMed. GGO: Ground-glass opacity.

MATERIALS AND METHODS

Literature search

We searched PubMed, EMBASE, OVID, EBSCO, and CNKI (China National Knowledge Infrastructure) databases without publication date or language restrictions, from inception to August 2015, using the search terms "CT", "computed tomography", "CT fluoroscopy", "CTF", "ground-glass opacity", "GGO", "lung", and "pulmonary". Search terms were present in the title or abstract of the articles. The detailed search strategy of PubMed is shown in Figure 1.

Study selection

A system documentation retrieval of human articles was accomplished by two independent observers to find out studies about the diagnostic value of CT fluoroscopy-guided PTNB in patients with GGO. All case reports, letters, comments, and review articles were eliminated. Subsequently, studies, on the basis of their title and abstract, was either included or discarded.

Studies that complied with the following criteria were also included in this study: (1) Adequate data to calculate the number of true positive (tp), false positive (fp), false negative (fn), and true negative (tn) results; (2) definite criteria to define a positive imaging result were documented; and (3) clinical follow-up or clinical observation for at least one year and/or surgery.

Other potentially eligible studies were identified by manually searching the reference lists of the articles enrolled in this meta-analysis. Any differences of opinion in selecting the studies between the two reviewers were resolved through discussion. If there was any unresolved studies advices were sought from another two reviewers experienced in study selection and data extraction in more than six meta-analyses or systematic reviews.

Data extraction

A 2 × 2 table was created to input following data extracted from each study included in the present meta-analysis: (1) true positive results (subjects with disease diagnosed correctly from the standard test); (2) false positive results (subjects without disease diagnosed as diseased from the standard test); (3) false negative results (subjects with disease diagnosed as without disease from the standard test); (4) true negative results (subjects without disease diagnosed correctly as without disease from the standard test); and (5) other clinical characteristics of the studies (including author, year of

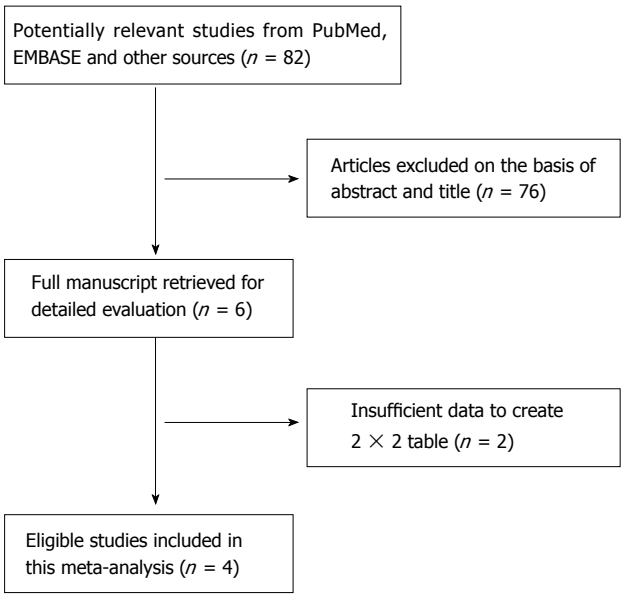


Figure 2 Flow chart of study selection.

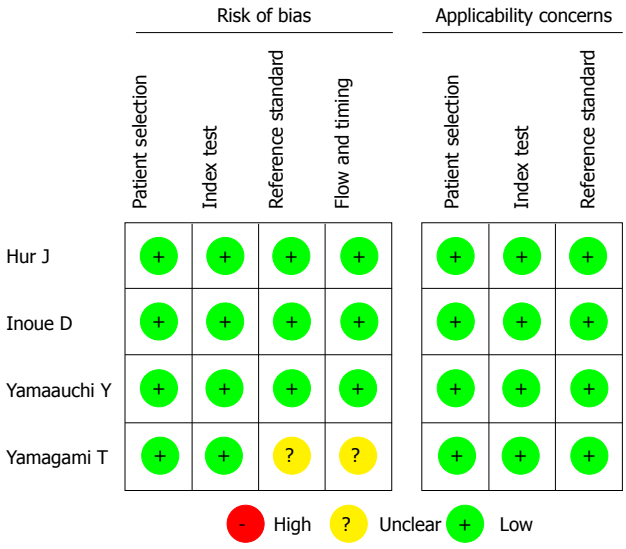


Figure 3 Quality assessment of diagnostic accuracy studies and criteria for included studies.

publication, lesion size, and complications).

Quality assessment

Methodological quality was evaluated on the basis of the Quality Assessment of Studies of Diagnostic Accuracy included on Systematic Reviews (QUADAS-2) guidelines independently by the same two reviewers who had performed the literature search. The quality of studies of diagnostic accuracy was specifically evaluated by the evidence-based tool above. Any dispute was resolved through discussion among the reviewers. A more detailed description of each item and a guideline on how to use the QUADAS-2 tool are provided by Whiting *et al*[10].

Statistical analysis

The data integration for the accuracy of CT fluoroscopy-guided PTNB for lung GGO lesions was made by calculating pooled estimates of sensitivity (Sen), specificity (Spe), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR) at a patient level. We also generated a summary receiver operating characteristic (SROC) curve as a way of summarizing the global test performance from different diagnostic studies. The pooled Sen, Spe, +LR, -LR, DOR, and SROC across studies were calculated by using a random or fixed effect model according to the heterogeneity. Heterogeneity across studies was evaluated by using the χ^2 and Fisher's exact tests. Threshold effect was assessed by using the Spearman rank correlation test. Subgroup analysis was also performed if necessary. Statistical analyses in this present meta-analysis were all carried out with Meta-disc software (version 1.4). $P < 0.05$ was considered statistically significant.

RESULTS

Study selection

Literature search revealed 82 articles which, after reading the titles and abstracts of the searched articles, 76 documents were discarded as they did not meet the inclusion criteria. After closer inspection of full text, 2 out of six were again discarded for the causes provided in Figure 2. Finally, the remaining four studies which fulfilled the inclusion criteria were included in this meta-analysis[6-9]. All 4 studies were published in English. Table 1 shows the basic characteristics of the included four studies. Methodological quality of the four studies, as evaluated by the QUADAS-2 tool, is shown in Figure 3.

Diagnostic accuracy

The pooled sensitivity with 95%CI was 0.91 (0.86-0.95), ranging from 0.71 to 0.88. However, the pooled specificity with 95%CI was 1.00 (0.91-1.00), and the specificities in the four studies were all reported as 1.00. The +LR, -LR and DOR with 95%CI was 18.64 (4.83-71.93), 0.11 (0.05-0.26), and 153.17 (30.78-762.33), respectively. χ^2 values of Sen, Spe, +LR, -LR, and DOR were 11.07 ($P = 0.01$), 0.0 ($P = 1.0$), 0.40 ($P = 0.94$), 11.14 ($P = 0.01$), and 0.84 ($P = 0.84$), respectively, indicating that there are some degree of heterogeneity among the four documents.

Forest plots (Figure 4) reveals the detailed sensitivity and specificity with 95%CI of each individual study. The detailed +LR and -LR with 95%CI for each individual study are shown in Forest plots (Figure 5). Figure 6 is the Forest plot of the DOR. The SROC curve showed a good overall diagnostic performance for CT fluoroscopy-guided PTNB for all studies combined (Figure 7). In this meta-analysis, Q-value of the maximum joint sensitivity and specificity was 0.94. The area under the SROC curve (AUC) was 0.98, which indicated a relatively high level of overall accuracy.

Subgroup analysis

Subgroup analysis was performed according to the size of the lesions and pooled indexes (Sen, Spe, +LR, -LR,

Table 1 Characteristics of the included four studies

Ref.	Year	Lesion size (mm)	tp	fp	fn	tn	All	Complications
Hur *et al*[6]	2009	≤ 10	4	0	2	4	10	Pneumothorax (5);
		11-20	5	0	2	3	10	Hemoptysis (3); Thoracostomy tube insertion (2)
		> 20	3	0	1	4	8	
		All	12	0	5	11	28	
Yamauchi *et al*[7]	2011	≤ 10	6	0	1	1	8	Pneumothorax (14); Hemoptysis (13); Thoracostomy tube
		11-20	36	0	1	5	42	insertion (0)
		> 20	17	0	0	0	17	
		All	59	0	2	6	67	
Inoue *et al*[8]	2012	≤ 10	21	0	1	2	24	Pneumothorax (30); Hemoptysis (7); Thoracostomy tube
		11-20	36	0	2	3	41	insertion (1);
		> 20	1	0	0	0	1	Air embolism (1)
		All	58	0	3	5	66	
Yamagami *et al*[9]	2013	≤ 10	16	0	4	11	31	Pneumothorax (44); Hemoptysis (9); Thoracostomy tube
		11-20	30	0	4	6	40	insertion (3)
		> 20	12	0	0	2	14	
		All	58	0	8	19	85	

fn: False negative; fp: False positive; tn: True negative; tp: True positive.

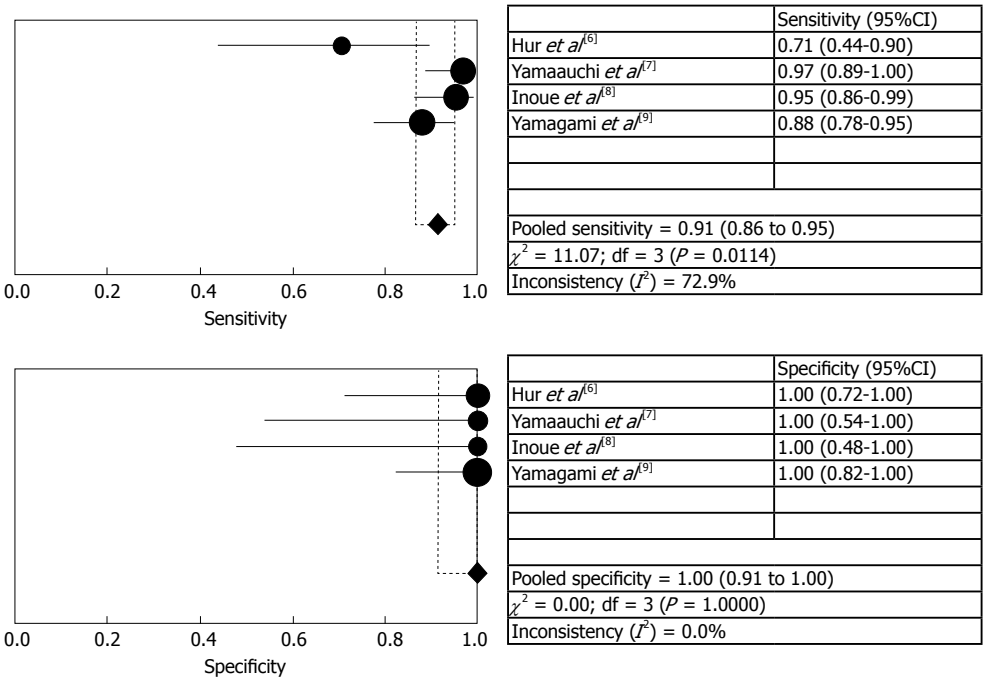


Figure 4 Forest plot shows sensitivity and specificity from individual studies and pooled estimates. Summary sensitivity and specificity were 0.91 (95%CI: 0.86-0.95) and 1.0 (95%CI: 0.91-1.00), respectively.

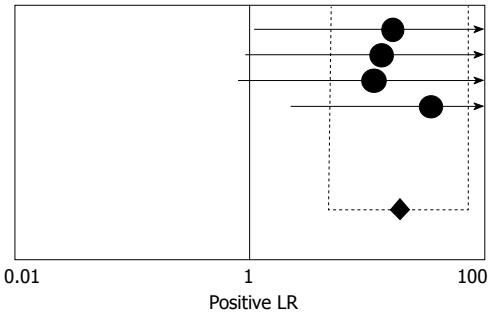
DOR and SROC) with 95%CI are summarized in Table 2.

Complications

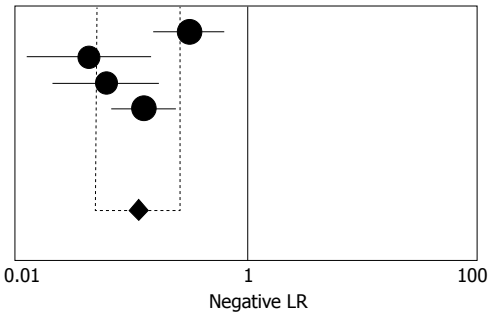
The incidence of pneumothorax ranged from 17.86% to 51.80%, and was reported in all four studies, with six patients requiring chest tube drainage. The incidence of hemoptysis ranged from 10.50% to 19.40% without any patients requiring treatment for it. Systemic air embolism occurred in one case as reported in the study by Inoue *et al*[8]. Apart from these, there were no other complications or adverse effects reported in the four studies included in the meta-analysis.

DISCUSSION

Bronchoscopy is one option for examination of patients with suspected lung masses. It can be used for tissue sampling, evaluating the nature and extent of a lung mass or a lesion and guiding therapy. However, in the case of a non-diagnostic bronchoscopy (*i.e.*, failure to obtain a histopathological diagnosis from lung lesion), image-guided PTNB is usually performed. Among these interventional techniques, lung biopsy under CT guidance has widespread acceptance as a preferred modality for the diagnosis of pulmonary masses. Its diagnostic

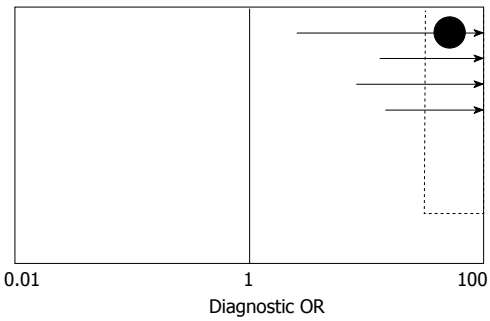


	Positive LR (95%CI)
Hur *et al*[6]	16.67 (1.09-255.73)
Yamaauchi *et al*[7]	13.44 (0.93-194.29)
Inoue *et al*[8]	11.32 (0.80-160.98)
Yamagami *et al*[9]	34.93 (2.26-540.06)
Fixed effects model	
Pooled positive LR = 18.64 (4.83 to 71.93)	
Cochran-Q = 0.40; df = 3 (P = 0.9399)	
Inconsistency (I^2) = 0.0%	



	Negative LR (95%CI)
Hur *et al*[6]	0.32 (0.16-0.65)
Yamaauchi *et al*[7]	0.04 (0.01-0.15)
Inoue *et al*[8]	0.06 (0.02-0.18)
Yamagami *et al*[9]	0.13 (0.07-0.24)
Random effects model	
Pooled negative LR = 0.11 (0.05 to 0.26)	
Cochran-Q = 11.14; df = 3 (P = 0.0110)	
Inconsistency (I^2) = 73.1%	
Tau-squared = 0.5068	

Figure 5 Forest plot shows positive likelihood ratio and negative likelihood ratio from individual studies and pooled estimates. Summary positive likelihood ratio (LR) and negative LR were 18.64 (95%CI: 4.83-71.93) and 0.11 (95%CI: 0.05-0.26), respectively.



	Diagnostic OR (95%CI)
Hur *et al*[6]	52.27 (2.59-1053.92)
Yamaauchi *et al*[7]	309.40 (13.36-7166.01)
Inoue *et al*[8]	183.86 (8.37-4038.39)
Yamagami *et al*[9]	268.41 (14.80-4867.71)
Fixed effects model	
Pooled diagnostic OR = 153.17 (30.78 to 762.33)	
Cochran-Q = 0.84; df = 3 (P = 0.8395)	
Inconsistency (I^2) = 0.0%	

Figure 6 Forest plot shows diagnostic odds ratio from individual studies and pooled estimates. Diagnostic odds ratio (OR) was 153.17 (95%CI: 30.78-762.33).

Table 2 Subgroup analysis of the included four studies

Size	Sen	Spe	+LR	-LR	DOR	SROC
All	0.91 (0.86-0.95)	1.0 (0.91-1.0)	18.64 (4.83-71.93)	0.11 (0.05-0.26)	153.17 (30.78-762.33)	0.98
≤ 10 mm	0.85 (0.73-0.94)	1.0 (0.81-1.0)	8.03 (2.21-29.18)	0.24 (0.14-0.41)	37.94 (7.48-192.37)	0.92
11-20 mm	0.92 (0.86-0.96)	1.0 (0.80-1.0)	9.35 (2.45-35.71)	0.13 (0.08-0.22)	67.98 (13.06-353.87)	0.96
> 20 mm	0.94 (0.70-1.0)	1.0 (0.54-1.0)	6.24 (0.97-40.0)	0.20 (0.07-0.60)[a]	38.93 (2.80-541.16)[b]	-[c]

[a,b]Only studies 6 and 9 were calculated; [c]SROC for GGO > 20 mm could not be calculated in this meta-analysis because of only two data points. Sen: Sensitivity; Spe: Specificity; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; DOR: Diagnostic odds ratio; SROC: Summary receiver operating characteristic; GGO: Ground-glass opacity.

accuracy is 92.9%-95% and the incidence of adverse effects is within an acceptable range[11-13]. Compared with techniques under conventional CT guidance, as it was reported, "CT fluoroscopy-guided PTNB allows continuous monitoring of the needle as it progresses toward the target lesion, enabling manipulation in response to respiratory movements"[14,15].

Nevertheless, diagnostic performance of PTNB under CT fluoroscopy guidance for the diagnosis of pulmonary GGO nodules is not well established. This meta-analysis investigated the overall diagnostic performance of CT fluoroscopy-guided PTNB in the differential diagnosis of GGO lesions with a high Sen and Spe, 0.91 (95%CI: 0.86-0.95) and 1.00 (95%CI: 0.91-1.00), respectively. The SROC curve stands for a global summary of test efficacy and indicates the trade-off between Sen and

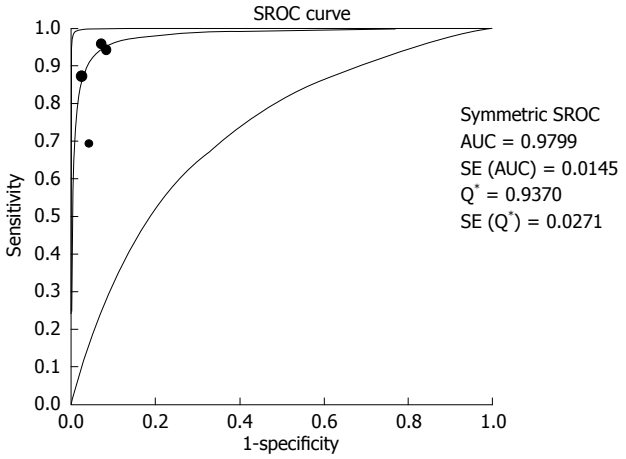


Figure 7 Summary receiver operating characteristic curve. SROC: Summary receiver operating characteristic.

Spe[16]. Our meta-analysis, according to the SROC curve, indicated that the maximum joint Sen and Spe was 0.94 and the AUC was 0.98, suggesting a high level of overall diagnostic efficacy. We conclude that CT fluoroscopy-guided PTNB plays an important role in the diagnosis of GGO lesions. DOR which, combines the data from Sen and Spe into a single value, is another reference of test accuracy[17]. In our meta-analysis, the DOR with 95%CI was 153.17 (30.78-762.33), indicating that CT fluoroscopy-guided PTNB was valuable in the diagnosis of GGO lesions. Subgroup analysis was performed according to the size of the lesions, and the pooled parameters were still good, indicating that CT fluoroscopy-guided PTNB was valuable in the diagnosis of GGO lesions regardless of their size.

The rate of complications was thought to be within an acceptable range. Pneumothorax, with an incidence of 17.86%-51.8%, was the most frequently encountered complication of CT fluoroscopy-guided PTNB[6-9]. Out of the 246 patients, only six required chest tube drainage. The incidence of hemoptysis ranged from 10.5% to 19.4%, without any of the patients requiring treatment. Yamagami *et al*[9], in the largest study, reported that the incidence of pneumothorax and hemoptysis was 51.8% and 10.6%, respectively. Inoue *et al*[8] reported one case of systemic air embolism. Even though an exact reason behind it could not be determined, there is a possibility of creating needle-induced fistula between the bronchus and the pulmonary vein in GGO lesion biopsy more than during solid lesion biopsy since GGO lesions preserve the bronchus and pulmonary vessels located inside them[8]. Hence, taking the results of Sen, Spe, DOR, +LR, and -LR into account, it is reasonable to think that CT fluoroscopy-guided PTNB can be used as one of the primary examination procedures for lung GGO lesions.

With respect to influencing factors for pneumothorax, there were significant differences reported, including patient age, sex, lesion location, number of pleural passages, and emphysema along the needle pathway[6-9,18]. Influencing factors for hemoptysis included patient age and sex, lesion location, nodule type, and distance from the pleura to the target lesion. Ground-glass nodules and deeper-located lesions were significant independent risk factors for hemoptysis[6-9,18]. In addition, the needle–pleural angle is another predictor of pneumothorax as reported by Li *et al*[19] and Niu *et al*[20]. De Filippo *et al*[21] reported that non-calcified density (the higher the density, the better the accuracy) was a positive predictive factor for diagnostic accuracy. The diagnostic performance of PTNB under CT guidance can be elevated by the use of multiplanar reformatting imaging, which is useful for planning the path of the needle while performing needle aspiration.

The diagnostic outcomes of conventional CT-guided lung biopsy have been studied previously. Kim *et al*[22] reported the outcomes of 50 patients (< 2.0 cm *vs* ≥ 2.0 cm and GGO component > 90% *vs* 50%-90%) who had been investigated with coaxial 18-gauge or 20-gauge core needles. The overall Sen, Spe, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were 92.0%, 90.0%, 97.0%, 75.0% and 91.0%, respectively. Sensitivity and accuracy were not significantly different between the two groups of lesion size and GGO components. Lu *et al*[23] reported the outcomes of 49 patients investigated with coaxial 20-gauge core needles. The overall Sen, Spe, PPV, NPV, and diagnostic accuracy were 93.62%, 100%, 100%, 40.0% and 93.88%, respectively. Compared to these results[22,23], we assume that the methodologies used in the included studies[6-9] (*i.e.*, the CT fluoroscopy and coaxial needle system) contributed to the high diagnostic accuracy observed.

This study is in accordance of the recommendation based upon the reporting of meta-analysis on diagnostic test[24]. We based this study on thorough literature searches and careful data extraction. Nevertheless, some limitations may be considered when interpreting the results. First, study includes only four articles. The limited number of patients (n = 246) may have an effect on our study. Second, the four studies did not compare directly the diagnostic accuracy of CT fluoroscopy-guided PTNB with other methods. Thus, we cannot definitively state which method is better at this time. However, studies by Rotolo *et al*[25] and Prosch *et al*[26] concluded that CT fluoroscopy systems for lung nodule biopsy are similar in terms of diagnostic performance and effective dose as cone-beam CT-guided and multislice CT systems. Finally, the publication format of four studies was English, which might resort to the so called "Tower of Babel" bias. In a word, further, larger prospective studies may be needed.

In conclusion, in spite of the difficulties mentioned above, considering the high diagnostic performance of CT fluoroscopy-guided PTNB in our study, along with the acceptable number of complications, we still have the reason to believe that this method can be recommended in clinical practice. In the end, update of systematic review and meta-analysis is possible only when further

research and data is available on this topic.

COMMENTS

Background

In recent years, as prevalence of lung cancer screening with low-dose computed tomography (CT) rises, so has the detection of pulmonary lesions that manifest as ground-glass opacity (GGO) nodules. Recently, several efforts utilizing percutaneous transthoracic needle biopsy (PTNB) under the guidance of CT fluoroscopy have been attempted to increase the diagnostic accuracy of lung GGO. Despite this, no consensus is available in the literature about whether it is beneficial to the patient.

Research frontiers

Because lung GGO is a nonspecific finding, it occurs in both malignant and benign lung lesions. Thus, the diagnosis of GGO lesions has become an important issue. Global research is directed towards an accurate and minimally invasive method for the diagnosis of lung GGO.

Innovations and breakthroughs

In this study, the authors investigated the value of CT fluoroscopy-guided PTNB for diagnosis of lung GGO. It is believed to be the first meta-analysis evaluating the value of CT fluoroscopy-guided PTNB for lung GGO.

Applications

The present study helps the authors understanding of the role of a minimally invasive technique for the diagnosis of lung GGO.

Peer-review

The aim of manuscript was to evaluate the value of CT fluoroscopy guided PTNB for the diagnosis of lung GGO with the use of meta-analysis method. The authors used the restrictive inclusion criteria, so only 4 manuscripts were included into analysis. Based on this they made some useful conclusions.

REFERENCES

1 **Hansell DM**, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**: 697-722 [PMID: 18195376 DOI: 10.1148/radiol.2462070712]

2 **Kaneko M**, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, Moriyama N. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201**: 798-802 [PMID: 8939234 DOI: 10.1148/radiology.201.3.8939234]

3 **Henschke CI**, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, Smith JP. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; **354**: 99-105 [PMID: 10408484 DOI: 10.1016/S0140-6736(99)06093-6]

4 **Collins J**, Stern EJ. Ground-glass opacity at CT: the ABCs. *AJR Am J Roentgenol* 1997; **169**: 355-367 [PMID: 9242736 DOI: 10.2214/ajr.169.2.9242736]

5 **Nakajima R**, Yokose T, Kakinuma R, Nagai K, Nishiwaki Y, Ochiai A. Localized pure ground-glass opacity on high-resolution CT: histologic characteristics. *J Comput Assist Tomogr* 2002; **26**: 323-329 [PMID: 12016356 DOI: 10.1097/00004728-200205000-00001]

6 **Hur J**, Lee HJ, Nam JE, Kim YJ, Kim TH, Choe KO, Choi BW. Diagnostic accuracy of CT fluoroscopy-guided needle aspiration biopsy of ground-glass opacity pulmonary lesions. *AJR Am J Roentgenol* 2009; **192**: 629-634 [PMID: 19234257 DOI: 10.2214/AJR.08.1366]

7 **Yamauchi Y**, Izumi Y, Nakatsuka S, Inoue M, Hayashi Y, Mukai M, Nomori H. Diagnostic performance of percutaneous core needle lung biopsy under multi-CT fluoroscopic guidance for ground-glass opacity pulmonary lesions. *Eur J Radiol* 2011; **79**: e85-e89 [PMID: 21515009 DOI: 10.1016/j.ejrad.2011.03.088]

8 **Inoue D**, Gobara H, Hiraki T, Mimura H, Kato K, Shibamoto K, Iishi T, Matsui Y, Toyooka S, Kanazawa S. CT fluoroscopy-guided cutting needle biopsy of focal pure ground-glass opacity lung lesions: diagnostic yield in 83 lesions. *Eur J Radiol* 2012; **81**: 354-359 [PMID: 21193278 DOI: 10.1016/j.ejrad.2010.11.025]

9 **Yamagami T**, Yoshimatsu R, Miura H, Yamada K, Takahata A, Matsumoto T, Hasebe T. Diagnostic performance of percutaneous lung biopsy using automated biopsy needles under CT-fluoroscopic guidance for ground-glass opacity lesions. *Br J Radiol* 2013; **86**: 20120447 [PMID: 23385998 DOI: 10.1259/bjr.20120447]

10 **Whiting PF**, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529-536 [PMID: 22007046 DOI: 10.7326/0003-4819-155-8-201110180-00009]

11 **Takeshita J**, Masago K, Kato R, Hata A, Kaji R, Fujita S, Katakami N. CT-guided fine-needle aspiration and core needle biopsies of pulmonary lesions: a single-center experience with 750 biopsies in Japan. *AJR Am J Roentgenol* 2015; **204**: 29-34 [PMID: 25539234 DOI: 10.2214/AJR.14.13151]

12 **Geraghty PR**, Kee ST, McFarlane G, Razavi MK, Sze DY, Dake MD. CT-guided transthoracic needle aspiration biopsy of pulmonary nodules: needle size and pneumothorax rate. *Radiology* 2003; **229**: 475-481 [PMID: 14595149 DOI: 10.1148/radiol.2291020499]

13 **Yeow KM**, Tsay PK, Cheung YC, Lui KW, Pan KT, Chou AS. Factors affecting diagnostic accuracy of CT-guided coaxial cutting needle lung biopsy: retrospective analysis of 631 procedures. *J Vasc Interv Radiol* 2003; **14**: 581-588 [PMID: 12761311 DOI: 10.1097/01.RVI.0000071087.76348.C7]

14 **Froelich JJ**, Ishaque N, Regn J, Saar B, Walthers EM, Klose KJ. Guidance of percutaneous pulmonary biopsies with real-time CT fluoroscopy. *Eur J Radiol* 2002; **42**: 74-79 [PMID: 12039025 DOI: 10.1016/S0720-048X(01)00391-6]

15 **Gianfelice D**, Lepanto L, Perreault P, Chartrand-Lefebvre C, Milette PC. Value of CT fluoroscopy for percutaneous biopsy procedures. *J Vasc Interv Radiol* 2000; **11**: 879-884 [PMID: 10928526 DOI: 10.1016/S1051-0443(07)61805-3]

16 **Walter SD**. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. *Stat Med* 2002; **21**: 1237-1256 [PMID: 12111876 DOI: 10.1002/sim.1099]

17 **Glas AS**, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129-1135 [PMID: 14615004 DOI: 10.1016/S0895-4356(03)00177-X]

18 **Hiraki T**, Mimura H, Gobara H, Iguchi T, Fujiwara H, Sakurai J, Matsui Y, Inoue D, Toyooka S, Sano Y, Kanazawa S. CT fluoroscopy-guided biopsy of 1,000 pulmonary lesions performed with 20-gauge coaxial cutting needles: diagnostic yield and risk factors for diagnostic failure. *Chest* 2009; **136**: 1612-1617 [PMID: 19429718 DOI: 10.1378/chest.09-0370]

19 **Li Y**, Du Y, Yang HF, Yu JH, Xu XX. CT-guided percutaneous core needle biopsy for small (≤20 mm) pulmonary lesions. *Clin Radiol* 2013; **68**: e43-e48 [PMID: 23177650 DOI: 10.1016/j.crad.2012.09.008]

20 **Niu XK**, Bhetuwal A, Yang HF. CT-guided core needle biopsy of pleural lesions: evaluating diagnostic yield and associated complications. *Korean J Radiol* 2015; **16**: 206-212 [PMID: 25598692 DOI: 10.3348/kjr.2015.16.1.206]

21 **De Filippo M**, Saba L, Concari G, Nizzoli R, Ferrari L, Tiseo M, Ardizzoni A, Sverzellati N, Paladini I, Ganazzoli C, Sconfienza LM, Carrafiello G, Brunese L, Genovese EA, Ampollini L, Carbognani P, Rusca M, Zompatori M, Rossi C. Predictive factors of diagnostic accuracy of CT-guided transthoracic fine-needle aspiration for solid noncalcified, subsolid and mixed pulmonary nodules. *Radiol Med* 2013; **118**: 1071-1081 [PMID: 23856805 DOI: 10.1007/s11547-013-0965-4]

22 **Kim TJ**, Lee JH, Lee CT, Jheon SH, Sung SW, Chung JH, Lee KW. Diagnostic accuracy of CT-guided core biopsy of ground-

glass opacity pulmonary lesions. *AJR Am J Roentgenol* 2008; **190**: 234-239 [PMID: 18094317 DOI: 10.2214/AJR.07.2441]

23 **Lu CH**, Hsiao CH, Chang YC, Lee JM, Shih JY, Wu LA, Yu CJ, Liu HM, Shih TT, Yang PC. Percutaneous computed tomography-guided coaxial core biopsy for small pulmonary lesions with ground-glass attenuation. *J Thorac Oncol* 2012; **7**: 143-150 [PMID: 22124475 DOI: 10.1097/JTO.0b013e318233d7dd]

24 **Deeks JJ**. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001; **323**: 157-162 [PMID: 11463691 DOI: 10.1136/bmj.323.7305.157]

25 **Rotolo N**, Floridi C, Imperatori A, Fontana F, Ierardi AM, Mangini M, Arlant V, De Marchi G, Novario R, Dominioni L, Fugazzola C, Carrafiello G. Comparison of cone-beam CT-guided and CT fluoroscopy-guided transthoracic needle biopsy of lung nodules. *Eur Radiol* 2016; **26**: 381-389 [PMID: 26045345]

26 **Prosch H**, Stadler A, Schilling M, Bürklin S, Eisenhuber E, Schober E, Mostbeck G. CT fluoroscopy-guided vs. multislice CT biopsy mode-guided lung biopsies: accuracy, complications and radiation dose. *Eur J Radiol* 2012; **81**: 1029-1033 [PMID: 21752567 DOI: 10.1016/j.ejrad.2011.01.064]

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META-ANALYSIS

Helicobacter pylori infection and asthma: Is there a direct or an inverse association? A meta-analysis

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Abstract

AIM: To analyze the consistency of a potential involvement of the bacterium infection in the asthma disease.

METHODS: A systematic literature search of the terms "*Helicobacter pylori*" (*H. pylori*) associated to "asthma" using PubMed, Scopus and the Cochrane Library Central was performed. Reference lists from published articles were also employed. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles. The criteria of inclusion of the studies were: Original studies; the *H. pylori* diagnostic method has been declared; all ranges of age have been included in our study; a definitive diagnosis of asthma has been reported.

RESULTS: We selected 14 articles in which the association between the two conditions was addressed. In 7 studies the prevalence of *H. pylori* infection in the asthma population and in the control population was made explicit. There was heterogeneity between the studies (Cohran's Q = 0.02). The *H. pylori* infection in the asthma population resulted 33.6% (518 of 1542), while in the control population resulted 37.6% (2746 of 7310) (relative risk of *H. pylori* infection in the asthma population = 0.87, 95%CI: 0.72-1.05, *P* = 0.015, random effects model). Instead, considering the more

virulent strains, the majority of studies showed an inverse relationship between the prevalence of *H. pylori* infection and asthma.

CONCLUSION: In our meta-analysis the prevalence of *H. pylori* infection in the asthma population resulted not statistically significant lower than in control population (P = 0.15). Instead, considering the more virulent strains, the majority of studies showed an inverse relationship between the prevalence of *H. pylori* infection and asthma.

Key words: Allergic diseases; Asthma; Extragastric manifestations; *Helicobacter pylori*; Hygiene

Core tip: The relationship between *Helicobacter pylori* infection and asthma is an important issue, since it could influence the choice of treatment. In our meta-analysis the prevalence of the infection in the asthma population resulted not statistically significant lower than in control population.

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INTRODUCTION

Asthma is a common respiratory disease, manifested by inflammatory and obstructive processes, secondary to multiple stimuli[1].

The etiology of asthma remains largely unclear. In the latest decades the prevalence of allergic asthma increased in children[2]. The reason is unknown. Changes in personal or maternal smoking habits, types of dwelling, adaptation to Western dietary habits, less infections, as a consequence of vaccinations, decreased family size and hygiene[3], air pollution, work exposure or changed microbiota due to occidental style of life[4] might be possible causes[5]. Some infectious agents, that affect specific organs, can also cause systemic diseases. Hence, it has been postulated that infections drive the differentiation of T helper (Th) cells to the Th1 subtype with resulting suppression of the Th2 subtype, involved in IgE-mediated allergy[3,6]. However, the theory that some infections in early childhood may prevent atopic sensitization (the "hygiene hypothesis")[7] is hotly debated[8].

The *Helicobacter pylori* (*H. pylori*) is a gram-negative, spiral shape, mobile, microaerophilic bacillus[9] that we can find in all over the world[10]. The *H. pylori* infection is chronic and the humans are infected in the first 10 years of age, especially in children living in family with a low socio-economic status. In the latest two decades links between *H. pylori* infection and extragastric manifestations have been reported[11]. The diseases in which a possible role of *H. pylori* has been hypnotized are cardiovascular diseases, hepatic diseases, skin diseases, rheumatologic diseases, blood diseases, *etc*[12,13].

The present review attempts to highlight the data regarding a potential link between *H. pylori* and asthma[14].

MATERIALS AND METHODS

Literature search

PRISMA statement guidelines were followed for conducting and reporting meta-analysis data[15]. PICOS scheme was followed for reporting inclusion criteria.

A MEDLINE, Scopus and the Cochrane Library Central query "*Helicobacter pylori*" or "*Helicobacter*" and "asthma" was performed. Reference lists from published articles were also employed. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles. The last access was dated March 12, 2016. Articles not in English were read by a specific native speaker.

Study selection

The criteria of inclusion of the studies were: (1) original studies; (2) the *H. pylori* diagnostic method has been declared; (3) all ranges of age have been included in our study; and (4) a definitive diagnosis of asthma has been reported.

Data extraction

Two authors (Fagoonee S and Colombini J) independently reviewed the literature search results and selected relevant studies. The full-text studies were assessed by the two authors to determine whether the inclusion criteria were met[16].

Risk of bias

The quality of each study was defined on the basis of the following criteria: (1) selection of patients and controls; (2) methods used to diagnose *H. pylori* infection; (3) diagnostic method of respiratory disease; (4) type of statistical analyses performed; and (5) adjustment for confounding factors. Data abstraction and an estimate of the quality were performed independently by all the authors, who compared the results and then reached a consensus. Assessment was not blind to names and origins of the authors or publications.

A meta-analysis has been performed of the studies in which the percentage of *H. pylori* infection in the asthma population and in the control population was made explicit.

Statistical analysis

When heterogeneity was present the random effects model was preferred to the fixed effects model. Cohran's

Table 1 Association between *Helicobacter pylori* infection and Asthma in paediatric population

Ref.	Method for assessing *H. pylori* infection	Association	No. of asthmatic/ No. of control	Age	Quality
Annagür *et al*[17]	Serological	Seropositivity was similar in acute exacerbations and stable asthmatics	79/36	5-15	3/5
Zevit *et al*[18]	^{13}C-urea breath test	Inverse association between *H. pylori* and pediatric asthma	578/6381	5-18	5/5
Khamechian *et al*[19]	Biopsy samples	Inverse association between *H. pylori* and pediatric asthma	36/264	5-18	4/5
Karimi *et al*[20]	^{13}C-urea breath test	Similar prevalence in cases and controls	98/98	< 18	2/5
den Hollander *et al*[4]	Serological	Positive association between *H. pylori* CagA- and pediatric asthma	3062/0	6	3/5

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A.

Q was used to test the heterogeneity and a P value < 0.1 was used as a cut-off for significance.

The results of the different studies, with 95%CI, and the overall effect with 95%CI, were illustrated in a forest plot graph; the pooled effects have been represented using a diamond.

A Freeman-Tukey transformation was used to calculate the weighted summary "proportion". The Mantel-Haenszel method was used for calculating the weighted pooled "relative risk". Statistical analyses were conducted using Med Calc® version 14.8.1 software. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Study selection

The search identified 169 publications. We read the abstracts of all articles and selected the 14 original papers where the inclusion criteria were met.

Epidemiology of the association

Pediatric population: Five studies included children with diagnosed asthma (Table 1) and in one study was described children with wheezing but not with a clear diagnosis of asthma: (1) in a monocentric, sample size: 115 participants (79 cases), follow-up: 24 mo, case-control study (quality: 3/5) on a pediatric population, the authors found no positive correlation between IgM and IgG antibodies to *H. pylori* and acute exacerbation or stable asthma (P = 0.494 and P = 0.227 respectively)[17]; (2) in a monocentric, sample size: 6959 participants (578 cases), follow-up: 24 mo, observational study, performed using the ^{13}C-urea breath test (UBT) (quality: 5/5), an inverse association between *H. pylori* and pediatric asthma was found (OR = 0.79, 95%CI: 0.66-0.94). In this case, a diagnosis was searched in the medical records, thus minimizing familial biases[18]; (3) in a monocentric[19], sample size: 300 participants (38 cases), observational study, performed using biopsy samples (quality: 4/5), an inverse association between *H. pylori* and pediatric asthma was demonstrated (P < 0.005).

These results were not confirmed by two monocentric studies: (4) an Iranian study[20], sample size: 196 participants, follow-up: 13 mo, cross-sectional study (quality: 2/5) performed in 98 asthmatic Iranian children, that found a similar *H. pylori* prevalence in cases and controls; and (5) an European study[4], sample size: 3797, prospective (quality: 3/5) performed in 3062 children, was found an association between *H. pylori* and risk of asthma (OR = 1.75, 95%CI: 1.07-2.87); children infected by CagA- *H. pylori* strain had an increased risk of asthma (OR = 2.11, 95%CI: 1.23-3.60), while those affected by a CagA-positive strains were not (OR = 0.94, 95%CI: 0.32-2.79).

Moreover, a lower *H. pylori* infection rate in children with wheezing was found in Dutch children who participated in the allergy cohort study[21].

Adult population: Nine selected studies included adults (Table 2). All were conducted using serology to demonstrate *H. pylori* infection.

Two studies: (1) one performed in Scotland[3] (monocentric, sample size: 219 participants, 19 cases), follow-up: 360 mo, survey study) (quality: 3/5); (2) another in Hong Kong[22] (monocentric, sample size: 187 participants (90 cases), follow-up: 12 mo, observational study) (quality: 2/5), indicated that exposures to *H. pylori* was not linked with the development of asthma in adulthood; (3) in a Japanese group of hospitalized patients, Jun *et al*[14] (monocentric, sample size: 94 participants, 46 cases, follow-up: 13 mo, case-control study) (quality: 2/5) did not find difference in anti-*H. pylori* IgG seropositivity and in CagA IgG seropositivity between asthmatics and controls (socioeconomically-matched); (4) Chen *et al*[23] (follow-up: 72 mo, survey study) (quality: 3/5) included 7663 participants in which information on demographics and medical history of asthma was collected using in-person interviews and valid serologic testing for *H. pylori*. In patients infected with *H. pylori*-CagA$^+$ strains the prevalence of asthma were lower compared to uninfected subjects. Colonization by *H. pylori*-CagA$^+$ strains was inversely related to having had asthma only in patients with an age of 42 year of more younger and was also find an inverse association between childhood asthma and CagA$^+$ status; (5) similar results were found by the same authors in a following study[24] (sample size: 7412 participants, 946 cases, survey study) (quality: 3/5). They analyzed several subclasses of ages and included only subjects in the younger subclass: *H. pylori* infection seemed to be a protective factor against current or past asthma (OR = 0.49, 95%CI: 0.3-0.8); (6) another group (monocentric,

Table 2 Association between *Helicobacter pylori* infection and Asthma in adult population

Ref.	Method for assessing *H. pylori* infection	Association	No. of asthmatic/ No. of control	Age	Quality
Bodner *et al*[3]	Serological	Seropositivity was similar in cases and controls	19/190	39-45	3/5
Tsang *et al*[22]	Serological	Seropositivity was similar in cases and controls	90/97	42.6 ± 16	2/5
Jun *et al*[14]	Serological	Seropositivity was similar in cases and controls (also for CagA)	46/48	51.2 ± 12.4	2/5
Chen *et al*[23]	Serological	*H. pylori*$^+$ CagA$^+$ were less likely to have ever been diagnosed as having asthma	525/7058	Adults	3/5
Chen *et al*[24]	Serological	Statistical significance only in age 3-13 yr	946/6466	⩾ 3	3/5
Reibma *et al*[25]	Serological	*H. pylori*$^+$ CagA$^+$ were less likely to have ever been diagnosed as having asthma	318/208	18-64	3/5
Shiotani *et al*[26]	Serological	Seropositivity was similar in cases and controls	6/771	New university students	2/3
Fullerton *et al*[27]	Serological	Seropositivity was similar in cases and controls	62/151	44.6 ± 13.5	3/5
Lim *et al*[28]	Serological	Statistical significance only in age < 40 yr	359/14673	18-91	3/5

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A.

sample size: 526 participants, 318 cases, case-control study) (quality: 3/5) reported findings supporting data on the inverse association[25]. Only after adjustment for socio-economic status there was an inverse association between asthma and CagA$^+$ status (OR = 0.63, 95%CI: 0.41-0.98); (7) in a Japanese study[26] monocentric, sample size: 777 participants (6 cases), follow-up: 12 mo, observational cross-sectional study (quality: 2/5), newly enrolled university students with bronchial asthma, 24-year-old or younger, were all *H. pylori* negative; (8) no association between *H. pylori* seropositivity and asthma was found in an United Kingdom monocentric, sample size: 213 participants (62 cases), follow-up: 108 mo, cross-sectional study (quality 3/5) (OR = 1.09, 95%CI: 0.77-1.54)[27]; and (9) a monocentric, retrospective Korean study[28] (quality 3/5) enrolled subjects aged ⩾ 18 years who had health surveillance checkups, including the serum anti-*H. pylori* IgG level. This large scale study demonstrated an inverse relationship between *H. pylori* infection and asthma among adults < 40 years old.

Meta-analysis

In seven of the fourteen studies[3,14,17,19,20,24,25] has been reported both the prevalence of *H. pylori* infection in the asthma population and in the control population. There is heterogeneity between the studies (Cohran's Q = 0.02). The prevalence of *H. pylori* infection in the asthma population resulted 33.6% (518 of 1542), while the prevalence of *H. pylori* infection in the control population resulted 37.6% (2746 of 7310) (relative risk of *H. pylori* infection in the asthma population = 0.87, 95%CI: 0.72-1.05, *P* = 0.15, random effects model), difference not statistically significant. The forest plot is illustrated in Figure 1.

DISCUSSION

Potential pathogenetic mechanisms

In animal models, experimental infection with *H. pylori* during the neonatal period induced a protective effect against asthma[29].

In case of gastric colonization by *H. pylori*-CagA$^+$ strains, mucosal Tregs are higher in number, and mucosal levels of the immunomodulatory cytokine IL-10 may be higher compared to the case of colonization by *H. pylori*-CagA$^-$ strains[30-38].

Gastroesophageal reflux disease (GERD) could by a trigger to asthma symptoms[39]. Microaspiration of the gastric contents into the lung damages the bronchial mucosa, which results in mucosal inflammation and bronchial hyper-responsiveness. Diffuse gastric atrophy, a consequence of *H. pylori* infection, especially CagA$^+$ strains, is a protective factor against GERD[40]. Part of the lower prevalence of asthma in people affected by *H. pylori* infection could be justified by the lower prevalence of GERD in this patients and not by an immunologic shift to an Th2 phenotype.

Considering the available studies on the potential association between *H. pylori* and asthma, sources of heterogeneity can be identified.

Focusing on sample size, negative results obtained in the various studies, when a limited number of patients was examined, must be considered with caution for the possible risk of statistical ß error[41]. Another critical issue, on this matter, is represented by the fact that included populations are heterogeneous and this may have important repercussions: The differences observed could be due to an inadequate selection of the control group.

Methods for assessing *H. pylori* infection vary in sensitivity and specificity, which may result in misclassification of exposure to the bacteria. Focusing on methodologies employed, some may indicate a previous contact with the microorganism (serological tests) while others an infection under way (UBT, histology). Both kinds are useful when studying long-term processes in which the microorganism could have been the primum movens and its disappearance does not change the illness story. On the contrary, if its role in an acute attack is studied, it is more appropriate to search for the active infection.

In summary, in our meta-analysis a sample of 8852

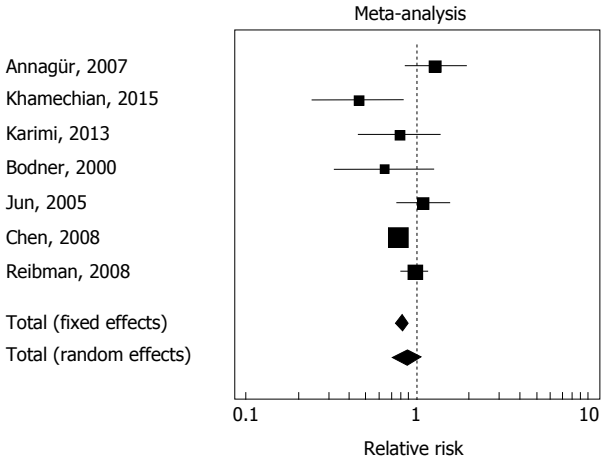

Figure 1 Relative risk of *Helicobacter pylori* population in the asthma population.

subjects are included and the prevalence of *H. pylori* infection in the asthma population resulted not statistically significant lower than in control population (relative risk = 0.87, P = 0.15).

The potential association between *H. pylori* infection and the reduction of risk of asthma development is an important issue in medicine, since it could influence the choice of bacterial treatment. The presence of *H. pylori* might be beneficial in childhood (decreasing risk of allergic diseases) but more deleterious later in life (increasing the risk of gastric adenocarcinoma).

Further prospective longitudinal studies with UBT for diagnosis of *H. pylori* are needed to prove a link between the lower prevalence of *H. pylori* infection and higher incidence of asthma.

COMMENTS

Background

Asthma is a common respiratory disease, manifested by inflammatory and obstructive processes, secondary to multiple stimuli. The etiology of asthma remains largely unclear. *Helicobacter pylori* (*H. pylori*) infection is a chronic one, generally acquired during childhood, and associated with lower socio-economic status.

Research frontiers

In the latest two decades, several studies have reported potential links between chronic *H. pylori* infection and a variety of extragastric manifestations. These include ischemic heart disease, liver diseases, skin diseases, rheumatic diseases, blood disorders, and others.

Innovations and breakthroughs

The present review attempts to highlight the data regarding a potential correlation between *H. pylori* infection and asthma.

Applications

The potential association between *H. pylori* infection and the reduction of risk of asthma development is an important issue in medicine, since it could influence the choice of bacterial treatment.

Peer-review

This is a well written meta-analysis paper concerning the elucidation of a potential involvement of *H. pylori* infection in the pathogenesis of asthma based on analysis of 14 papers selected from 169 publications.

REFERENCES

1 **Bell MC**, Busse WW. Severe asthma: an expanding and mounting clinical challenge. *J Allergy Clin Immunol Pract* 2013; **1**: 110-121; quiz 122 [PMID: 24565450 DOI: 10.1016/j.jaip.2013.01.005]

2 **Omran M**, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. *BMJ* 1996; **312**: 34 [PMID: 8555858 DOI: 10.1136/bmj.312.7022.34]

3 **Bodner C**, Anderson WJ, Reid TS, Godden DJ. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax* 2000; **55**: 383-387 [PMID: 10770819 DOI: 10.1136/thorax.55.5.383]

4 **den Hollander WJ**, Sonnenschein-van der Voort AM, Holster IL, de Jongste JC, Jaddoe VW, Hofman A, Perez-Perez GI, Moll HA, Blaser MJ, Duijts L, Kuipers EJ. Helicobacter pylori in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther* 2016: Epub ahead of print [PMID: 26932510 DOI: 10.1111/apt.13572]

5 **Matricardi PM**, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionne P, Stroffolini T, Pasquini P, D'Amelio R. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997; **314**: 999-1003 [PMID: 9112843 DOI: 10.1136/bmj.314.7086.999]

6 **Romagnani S**. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol* 1992; **98**: 279-285 [PMID: 1422257 DOI: 10.1159/000236199]

7 **Strachan DP**. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259-1260 [PMID: 2513902]

8 **Strachan DP**. Lifestyle and atopy. *Lancet* 1999; **353**: 1457-1458 [PMID: 10232306]

9 **Roussos A**, Philippou N, Gourgoulianis KI. Helicobacter pylori infection and respiratory diseases: a review. *World J Gastroenterol* 2003; **9**: 5-8 [PMID: 12508341 DOI: 10.3748/wjg.v9.i1.5]

10 **Thomas JE**, Dale A, Harding M, Coward WA, Cole TJ, Weaver LT. Helicobacter pylori colonization in early life. *Pediatr Res* 1999; **45**: 218-223 [PMID: 10022593 DOI: 10.1203/00006450-199902000-00010]

11 **Durazzo M**, Rosina F, Premoli A, Morello E, Fagoonee S, Innarella R, Solerio E, Pellicano R, Rizzetto M. Lack of association between seroprevalence of Helicobacter pylori infection and primary biliary cirrhosis. *World J Gastroenterol* 2004; **10**: 3179-3181 [PMID: 15457568 DOI: 10.3748/wjg.v10.i21.3179]

12 **Marietti M**, Gasbarrini A, Saracco G, Pellicano R. Helicobacter pylori infection and diabetes mellitus: the 2013 state of art. *Panminerva Med* 2013; **55**: 277-281 [PMID: 24088801]

13 **Pellicano R**, Franceschi F, Saracco G, Fagoonee S, Roccarina D, Gasbarrini A. Helicobacters and extragastric diseases. *Helicobacter* 2009; **14** Suppl 1: 58-68 [PMID: 19712170 DOI: 10.1111/j.1523-5378.2009.00699.x]

14 **Jun ZJ**, Lei Y, Shimizu Y, Dobashi K, Mori M. Helicobacter pylori seroprevalence in patients with mild asthma. *Tohoku J Exp Med* 2005; **207**: 287-291 [PMID: 16272799 DOI: 10.1620/tjem.207.287]

15 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; **6**: e1000100 [PMID: 19621070 DOI: 10.1371/journal.pmed.1000100]

16 **Miao XP**, Li JS, Ouyang Q, Hu RW, Zhang Y, Li HY. Tolerability of selective cyclooxygenase 2 inhibitors used for the treatment of rheumatological manifestations of inflammatory bowel disease. *Cochrane Database Syst Rev* 2014; **10**: CD007744 [PMID: 25340915 DOI: 10.1002/14651858.CD007744.pub2]

17 **Annagür A**, Kendirli SG, Yilmaz M, Altintas DU, Inal A. Is there any relationship between asthma and asthma attack in children and atypical bacterial infections; Chlamydia pneumoniae, Mycoplasma pneumoniae and Helicobacter pylori. *J Trop Pediatr* 2007; **53**: 313-318 [PMID: 17535826 DOI: 10.1093/tropej/fmm040]

18 **Zevit N**, Balicer RD, Cohen HA, Karsh D, Niv Y, Shamir R. Inverse association between Helicobacter pylori and pediatric asthma in a high-prevalence population. *Helicobacter* 2012; **17**: 30-35 [PMID: 22221613 DOI: 10.1111/j.1523-5378.2011.00895.x]

19 **Khamechian T**, Movahedian AH, Ebrahimi Eskandari G, Heidarzadeh Arani M, Mohammadi A. Evaluation of the Correlation Between Childhood Asthma and Helicobacter pylori in Kashan. *Jundishapur J Microbiol* 2015; **8**: e17842 [PMID: 26310565 DOI: 10.5812/jjm.8(6)2015.17842]

20 **Karimi A**, Fakhimi-Derakhshan K, Imanzadeh F, Rezaei M, Cavoshzadeh Z, Maham S. Helicobacter pylori infection and pediatric asthma. *Iran J Microbiol* 2013; **5**: 132-135 [PMID: 23825730]

21 **Holster IL**, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ, de Jongste JC, Kuipers EJ. The impact of Helicobacter pylori on atopic disorders in childhood. *Helicobacter* 2012; **17**: 232-237 [PMID: 22515362 DOI: 10.1111/j.1523-5378.2012.00934.x]

22 **Tsang KW**, Lam WK, Chan KN, Hu W, Wu A, Kwok E, Zheng L, Wong BC, Lam SK. Helicobacter pylori sero-prevalence in asthma. *Respir Med* 2000; **94**: 756-759 [PMID: 10955750 DOI: 10.1053/rmed.2000.0817]

23 **Chen Y**, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. *Arch Intern Med* 2007; **167**: 821-827 [PMID: 17452546 DOI: 10.1001/archinte.167.8.821]

24 **Chen Y**, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]

25 **Reibman J**, Marmor M, Filner J, Fernandez-Beros ME, Rogers L, Perez-Perez GI, Blaser MJ. Asthma is inversely associated with Helicobacter pylori status in an urban population. *PLoS One* 2008; **3**: e4060 [PMID: 19112508 DOI: 10.1371/journal.pone.0004060]

26 **Shiotani A**, Miyanishi T, Kamada T, Haruma K. Helicobacter pylori infection and allergic diseases: epidemiological study in Japanese university students. *J Gastroenterol Hepatol* 2008; **23**: e29-e33 [PMID: 17725593 DOI: 10.1111/j.1440-1746.2007.05107.x]

27 **Fullerton D**, Britton JR, Lewis SA, Pavord ID, McKeever TM, Fogarty AW. Helicobacter pylori and lung function, asthma, atopy and allergic disease--a population-based cross-sectional study in adults. *Int J Epidemiol* 2009; **38**: 419-426 [PMID: 19109248 DOI: 10.1093/ije/dyn348]

28 **Lim JH**, Kim N, Lim SH, Kwon JW, Shin CM, Chang YS, Kim JS, Jung HC, Cho SH. Inverse Relationship Between Helicobacter Pylori Infection and Asthma Among Adults Younger than 40 Years: A Cross-Sectional Study. *Medicine* (Baltimore) 2016; **95**: e2609 [PMID: 26937899 DOI: 10.1097/MD.0000000000002609]

29 **Arnold IC**, Dehzad N, Reuter S, Martin H, Becher B, Taube C, Müller A. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Invest* 2011; **121**: 3088-3093 [PMID: 21737881 DOI: 10.1172/JCI45041]

30 **Gasbarrini A**, Franceschi F, Gasbarrini G, Pola P. Extraintestinal pathology associated with Helicobacter infection. *Eur J Gastroenterol Hepatol* 1997; **9**: 231-233 [PMID: 9096420 DOI: 10.1097/00042737-199703000-00001]

31 **Codolo G**, Mazzi P, Amedei A, Del Prete G, Berton G, D'Elios MM, de Bernard M. The neutrophil-activating protein of Helicobacter pylori down-modulates Th2 inflammation in ovalbumin-induced allergic asthma. *Cell Microbiol* 2008; **10**: 2355-2363 [PMID: 18671823 DOI: 10.1111/j.1462-5822.2008.01217.x]

32 **Amedei A**, Cappon A, Codolo G, Cabrelle A, Polenghi A, Benagiano M, Tasca E, Azzurri A, D'Elios MM, Del Prete G, de Bernard M. The neutrophil-activating protein of Helicobacter pylori promotes Th1 immune responses. *J Clin Invest* 2006; **116**: 1092-1101 [PMID: 16543949 DOI: 10.1172/JCI27177]

33 **D'Elios MM**, Amedei A, Cappon A, Del Prete G, de Bernard M. The neutrophil-activating protein of Helicobacter pylori (HP-NAP) as an immune modulating agent. *FEMS Immunol Med Microbiol* 2007; **50**: 157-164 [PMID: 17521355 DOI: 10.1111/j.1574-695X.2007.00258.x]

34 **Oppmann B**, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, Vega F, Yu N, Wang J, Singh K, Zonin F, Vaisberg E, Churakova T, Liu M, Gorman D, Wagner J, Zurawski S, Liu Y, Abrams JS, Moore KW, Rennick D, de Waal-Malefyt R, Hannum C, Bazan JF, Kastelein RA. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 2000; **13**: 715-725 [PMID: 11114383]

35 **Robinson K**, Kenefeck R, Pidgeon EL, Shakib S, Patel S, Polson RJ, Zaitoun AM, Atherton JC. Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses. *Gut* 2008; **57**: 1375-1385 [PMID: 18467372 DOI: 10.1136/gut.2007.137539]

36 **Oertli M**, Müller A. Helicobacter pylori targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes* 2012; **3**: 566-571 [PMID: 22895083 DOI: 10.4161/gmic.21750]

37 **Maldonado RA**, von Andrian UH. How tolerogenic dendritic cells induce regulatory T cells. *Adv Immunol* 2010; **108**: 111-165 [PMID: 21056730 DOI: 10.1016/B978-0-12-380995-7.00004-5]

38 **Harris PR**, Wright SW, Serrano C, Riera F, Duarte I, Torres J, Peña A, Rollán A, Viviani P, Guiraldes E, Schmitz JM, Lorenz RG, Novak L, Smythies LE, Smith PD. Helicobacter pylori gastritis in children is associated with a regulatory T-cell response. *Gastroenterology* 2008; **134**: 491-499 [PMID: 18242215 DOI: 10.1053/j.gastro.2007.11.006]

39 **Kahrilas PJ**, Smith JA, Dicpinigaitis PV. A causal relationship between cough and gastroesophageal reflux disease (GERD) has been established: a pro/con debate. *Lung* 2014; **192**: 39-46 [PMID: 24221340 DOI: 10.1007/s00408-013-9528-7]

40 **Vicari JJ**, Peek RM, Falk GW, Goldblum JR, Easley KA, Schnell J, Perez-Perez GI, Halter SA, Rice TW, Blaser MJ, Richter JE. The seroprevalence of cagA-positive Helicobacter pylori strains in the spectrum of gastroesophageal reflux disease. *Gastroenterology* 1998; **115**: 50-57 [PMID: 9649458 DOI: 10.1016/S0016-5085(98)70364-6]

41 **Gambino SR**, Galen RS. "Alpha" and "beta" errors. *Clin Chem* 1983; **29**: 1319 [PMID: 6851124]

P- Reviewer: Abadi ATB, Nakajima N, Slomiany BL, Tosetti C, Tovey FI, Vorobjova T **S- Editor**: Ji FF
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META-ANALYSIS

Efficacy, safety, and dose comparison of degarelix for the treatment of prostate cancer: A systematic review and meta-analysis

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Abstract

AIM: To conduct a systematic review and meta-analysis into the efficacy, safety, and dosage regimens of degarelix for treating prostate cancer (PCa).

METHODS: PubMed, EMBASE, the Cochrane Library, and Web of Science was systematically searched to identify randomized controlled trials (RCTs) comparing degarelix (240/80 mg *vs* 240/160 mg) to the gonadotropin-releasing hormone agonists, goserelin and leuprolide, for the treatment of PCa. Two independent reviewers screened putative studies, assessed the risk of bias, and then extracted pertinent data. Analyses were performed using Review Manager 5.2.

RESULTS: Seven papers from six RCTs, involving 1204 patients, were identified. The present meta-analysis showed that treatment with 240/160 mg degarelix is more effective and has fewer adverse events (AEs) relative to conventional 240/80 mg regimen. Degarelix significantly decreased International Prostate Symptom Scores [standardized mean differences (SMD) = -0.32, 95%CI: -0.51 to -0.12, P = 0.02] and caused fewer AEs (SMD = -0.28, 95%CI: -0.48 to -0.07, P = 0.008) than goserelin. Degarelix suppressed testosterone and prostate-specific antigen significantly faster than leuprolide.

CONCLUSION: Degarelix is a useful option in the treatment of advanced PCa. Degarelix 240/160 mg

regimen was superior to a 240/80 mg regimen. More rigorously designed RCTs are urgently needed to confirm the efficacy of degarelix.

Key words: Prostate cancer; Degarelix; Meta-analysis

Core tip: This meta-analysis and systematic review aimed to compare the efficacy, safety, and dosage regimens of degarelix for prostate cancer. A total of seven papers from 6 randomized controlled trials were identified, involving 1204 patients. Degarelix was an useful option in the treatment of advanced prostate cancer, and degarelix 240/160 mg regimen was superior to 240/80 mg regimen.

Fang C, Wu CL, Liu SS, Ge L, Bai JL. Efficacy, safety, and dose comparison of degarelix for the treatment of prostate cancer: A systematic review and meta-analysis. *World J Meta-Anal* 2016; 4(3): 69-76 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i3/69.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i3.69

INTRODUCTION

Prostate cancer (PCa) is one of the most common malignant neoplasm in men. The mortality rates associated with PCa has reduced in many developed countries due to improvements in curative treatment[1]. However, the incidence of PCa and related mortality rates are increasing in many developing countries[1-3].

PCa is hormone-sensitive[4] and is the most common initial treatment regime for PCa is androgen deprivation therapy (ADT)[5]. Androgen deprivation may be achieved by either surgical or medical intervention[4]. Gonadotropin-releasing hormone (GnRH) agonists and antagonists have been approved for ADT in treating advanced PCa[6]. GnRH agonists and antagonists ultimately act by suppressing testosterone to castration levels[7]. GnRH antagonists bind directly to GnRH receptors, blocking the effect of GnRH on the pituitary, producing an immediate suppression of luteinising hormone, follicle stimulating hormone, and testosterone. GnRH antagonists are likely to replace GnRH agonists as first-line ADT in the future[8].

Degarelix, a GnRH antagonist and first-line therapy for androgen-sensitive advanced PCa, causes a rapid and sustained testosterone suppression to castrate levels without a surge[6]. Degarelix has demonstrated a significantly superior progression-free survival and overall survival rates related to GnRH agonists in a recent pooled individual patient data analysis[9]. The conventional monthly degarelix regimen of 240/80 mg (initial dosage/maintenance dosage) has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[10]. The results of phase Ⅱ and Ⅲ studies show that the efficacy and safety of the 240/80 mg and 240/160 mg degarelix regimens are not markedly different[10,11]. However, the dosage-funding study by Van Poppel *et al*[12] suggested a regimen of dosage 240 mg and 160 mg is preferred.

The study aims to conduct a systematic review and meta-analysis to compare the efficacy and safety of degarelix (240/80 mg and 240/160 mg) *vs* GnRH agonists for the treatment of advanced PCa.

MATERIALS AND METHODS

Search strategy

PubMed (1966-July 2014), EMBASE.com (1974-July 2014), Cochrane Library (CENTRAL, Issue 6 of 12, June 2014), and Web of Science (2000 - July 2014) were searched to identified all relevant RCTs, the search was performed in July 8, 2014. No restrictions as to language, publication data, and publication status were applied. The search strategy was independently conducted by two reviewers. And the search strategy of PubMed is following: ["Prostatic Neoplasms"(Mesh) OR "Prostatic Neoplasms, Castration-Resistant" (Mesh)] OR [prostatic cancer* OR prostatic tumor* OR prostatic carcinoma* OR prostatic neoplasm* OR prostate cancer* OR prostate tumor* OR prostate carcinoma* OR prostate neoplasm* (Title/Abstract)] AND ["acetyl-2-naphthylalanyl-3-chlorophenylalanyl-1-oxohexadecyl-seryl-4-aminophenylalanyl(hydrooroty l)-4-aminophenylalanyl(carbamoyl)-leucyl-ILys-prolyl-alaninamide" (Supplementary Concept) OR degarelix OR firmagon] AND [random* OR randomized con–trolled trial* OR randomized trial* OR Randomized Controlled Trial(ptyp) OR "Randomized Controlled Trials as Topic"]. We also tracked the references of included studies and reviews to find potentially eligible studies.

Inclusion criteria

RCTs met the following criteria were included: (1) study participants were ⩾ 18 years old, had a histological confirmation of PCa (all stages), for whom endocrine treatment was indicated, and any previous or current hormonal management of PCa had been discontinued for > 6 mo before enrolment; (2) RCT or "random group" was mentioned in the methodology section; and (3) reported outcomes included the mean percentage changes of total prostate volume (TPV), quality of life (QoL) related to urinary symptoms, International Prostate Symptom Score (IPSS), adverse events (AEs), the testosterone response rates (cumulative proportion of patients with serum testosterone suppression ⩽ 0.5 ng/mL), the incidence of prostate-specific antigen (PSA) failure (defined as an increase in PSA of ⩾ 50% from nadir or ⩾ 5 ng/mL on two consecutive occasions at least two weeks apart), the incidence of death, and PSA, luteinizing hormone (LH), follicle-stimulating hormone (FSH) level.

Exclusion criteria were studies reporting: (1) on

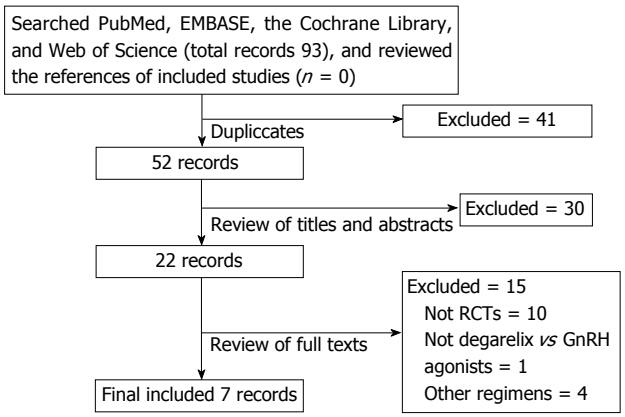

Figure 1 The details of identifying studies. RCT: Randomized controlled trials; GnRH: Gonadotropin-releasing hormone.

patients who had received hormonal treatments for PCa within 6 mo; (2) where the intervention was not degarelix; and (3) animal studies, case-reports, reviews, abstracts, corres or letters to the journal editors.

Two reviewers independently examined studies for eligibility according to the eligibility criteria. Conflicts were resolved by a third reviewer.

Data extraction and quality assessment

A standard data extraction form was designed, which included fields for the first authors, publication year, intervention regimen, study size, tumor stage, Gleason score, dosage, duration, and outcomes. The methodological quality was evaluated according to the Cochrane Handbook version 5.1.0[13], namely on criteria of: Random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other biases. Judgments for each entry involved stratifying the risk of bias as "low risk", "high risk", or "unclear risk". Data extraction and quality assessment were performed by two independent reviewers, conflicts were resolved by a third reviewer.

Statistical analysis

The standardized mean differences (SMD) with 95%CI were calculated for continuous variables (mean percentage changes of TPV, mean IPSS). OR with 95%CI were calculated for dichotomous variables (AEs, *etc.*). The heterogeneity between trials was evaluated using c^2 statistic, where an $I^2 \leqslant 50\%$ and a *P*-value $\geqslant 0.10$ was indicative of no statistical heterogeneity, upon which a fixed-effects model was applied. All analyses were conducted using Review Manager 5.2 software.

RESULTS

Search results

A total of 93 studies were identified. Forty-one studies were excluded duo to duplication. After screening the title and abstract of the remaining 52 studies, 30 studies were excluded for not being a RCT, not involving degarelix, not treating PCa, or for being an abstract, letter. After screening the full-text versions of 22 studies, 7 studies were excluded for not being a RCT (n = 3), for not reporting on degarelix *vs* GnRH agonists (n = 1) or 240/80 mg *vs* 240/160 mg regimens (n = 4), or for reporting identical results as a previous RCT (n = 3), or for being a review (n = 2) or a cost-effectiveness analysis (n = 2). Finally, 7 papers reporting on 6 RCTs, involving 1204 patients, were included in the present meta-analysis. The details of identifying studies could be found in Figure 1. Three RCTs reported on degarelix *vs* goserelin[14-16], 1 on degarelix *vs* leuprolide[11], and 3 on 240/80 mg *vs* 240/160 mg degarelix regimens[10-12]. The baseline characteristics are presented in Table 1.

Methodological quality assessment

All of the included RCTs were conducted using a multicenter, randomized, parallel-group, open-label, comparative design. Only 2 studies mentioned the methods of randomization and allocation concealment (a validated computer program and central allocation, respectively). However, all 6 of the RCTs failed to report the use of blinding. All studies were considered low risk for selective reporting (Table 2).

Meta-analysis of degarelix vs goserelin

Mean percentage changes of TPV: Three studies[14-16], involving 463 patients, reported TPV. The results of heterogeneity evaluation between the three studies showed that I^2 was 57%, P = 0.10. The results were modelled with random effects. The efficacy of degarelix in terms of mean percentage decreases in TPV was similar to that of goserelin (SMD = -0.10; 95%CI: -0.43 to 0.23; P = 0.56; Figure 2).

QoL related to urinary symptoms: Three studies[14-16], involving 463 patients, reported on QoL. The heterogeneity (I^2) between three studies was I^2 = 76% (P = 0.02). The results were modelled with random effects. The improvement of QoL related to urinary symptoms in degarelix group was similar to goserelin (SMD = -0.391; 95%CI: -0.83 to 0.06; P = 0.09; Figure 2).

Mean IPSS and IPSS $\geqslant$ 13: The mean decrease of IPSS scores from baseline level were reported in three studies[14-16]. A fixed-effect model was used for meta-analysis since there was no statistical heterogeneity (I^2 = 0%; P = 0.91). The mean decrease in IPSS scores in the degarelix group was significantly greater than in the goserelin group (SMD = -0.32; 95%CI: -0.51 to -0.12; P = 0.02; Figure 3). The heterogeneity (I^2) between the two studies for a decrease in IPSS of $\geqslant$ 13 (moderate/severe) from baseline level was I^2 = 0% (P = 0.78). After a fixed-effect model was applied, the results of the meta-analysis indicated that the decrease in IPSS $\geqslant$ 13 was greater in the degarelix group than within the goserelin group (SMD = -0.28; 95%CI: -0.48 to -0.07; P = 0.008; Figure 3).

Changes from baseline in serum testosterone and PSA: Three studies[14-16] reported the levels of testosterone

Table 1 Baseline characteristics of included studies

Ref.	Study arms (dose, Initial dose (mg)/monthly maintenance dosage (mg)	Regimen	Sample	Age (yr)	BMI (kg/m^2)	T stage		Tumour stage				Gleason score			ECOG (≤ 2)	Duration (mo)
						T1/2	T3/4	Localized	Locally advanced	Metastatic	Not classifiable	2-6	7	8-10		
Axcrona *et al*[14]	Degarelix (240/80)	Monthly	82	71.9 ± 7.7	26.8 ± 4.1	35	47	24	30	22	6	17	24	41	82	3
	Goserelin (3.6)	Goserelin 12 wk + 50 mg/d bicalutamide during the initial 28 d	97	73.0 ± 7.1	26.5 ± 3.7	42	55	32	23	31	11	16	31	50	96	
Anderson *et al*[15]	Degarelix (240/80)	240 mg for 1 mo, 80 mg/mo	27	68 (53-87)	NR	5	21	NR				2	25		27	3
	Goserelin (3.6)	3.6 mg/mo goserelin + 50 mg/d bicalutamide	13	72 (57-85)	NR	2	11					0	13		13	
Mason *et al*[16]	Degarelix (240/80)	240 mg day 0 + 80 mg day 28 and 56	180	70.6 ± 6.37	27.8 ± 3.99	116	64	111	63	NR	6	41	97	42	180	3
	Goserelin (3.6)	Goserelin 3.6 mg day 3, 31 and 59	64	70.8 ± 5.96	26.8 ± 3.69	42	21	41	20	NR	3	12	42	10	64	
Klotz L *et al*[11]	Degarelix (240/80, 240/160)	240 mg for 1 mo + 80/160 mg monthly	207	72 (51-89)	26.7 ± 4.2	69	64	69	64	37	37	88	63	56	195	12
	Leuprolide (7.5)	Leuprolide 7.5 mg/mo	201	74 (50-88)	26.9 ± 3.9	63	52	63	52	47	39	87	62	51	190	
Ozono *et al*[10]	Degarelix (240/80)	240 mg/dose + 80 mg/mo	136	74.7 ± 6.76	NR	61	42	61	42	33	0	19	117		NR	12
	Degarelix (240/160)	240 mg/dose + 160 mg/mo	137	74.2 ± 7.19	NR	64	41	64	41	31	1	23	114		NR	
Van Poppel *et al*[12]	Degarelix (240/80)	240 mg/dose + 80 mg/mo	30	70 (57-88)	26 (18-41)	5	12	5	12	5	8	19	11		NR	12
	Degarelix (240/160)	240 mg/dose + 160 mg/mo	30	73 (52-82)	25 (20-30)	5	10	5	10	7	8	15	15		NR	

BMI: Body mass index; ECOG: European Cooperative Oncology Group; NR: Not reported.

and PSA. All patients within the degarelix group maintained serum testosterone at or below castrate levels (0.5 ng/mL) at 4, 8 and 12 wk. Patients within the goserelin group, however, only achieved castrate levels of serum testosterone at 8 and 12 wk. Mean PSA levels at 12 wk were reduced by 91.07% in the degarelix group and by 95.77% within the goserelin group. There were no differences between the two groups for serum testosterone and PSA levels.

Systematic review of degarelix vs leuprolide

The present search strategy only identified one RCT[11] comparing the use of degarelix (240/80 mg) *vs* leuprolide (7.5 mg) for the treatment of PCa. The testosterone response rates from day 28 through day 364 were similar between degarelix and leuprolide groups (97.2% *vs* 96.4%; P = 0.53). By day 3, the median testosterone levels were ≤ 0.5 ng/mL in 96.1% in the degarelix groups. By contrast, the median testosterone levels increased by 65% from baseline by day 3 in the leuprolide groups (median testosterone level 6.30 ng/mL; P < 0.001). The median rate of decrease in PSA levels up to day 14 and day 28 were greater in degarelix groups than in the leuprolide group (64% *vs* 18% and 85% *vs* 68%, respectively). The incidence of PSA failure was higher in the degarelix than within the goserelin groups (8.70% *vs* 13.93%; P = 0.10). The median reduction in FSH at the day 364 compared with baseline levels were 88.50% and 54.8% within the degarelix and goserelin groups, respectively.

Meta-analysis of degarelix 240/80 mg vs 240/160 mg

The testosterone response rates from day 28 through to day 364: Three studies[10-12] reported this outcome. There was no statistical heterogeneity between these three studies (I^2 = 0%; P = 0.93). The data was modelled with fixed-effects. There were no statistical differences for two groups in the testosterone response rates (OR = 0.75; 95%CI: 0.33-1.73; P = 0.51; Figure 4).

The testosterone response rates at day 3 and the incidence of PSA failure: Two studies[10,11] reported these outcomes. The heterogeneity (I^2) between the studies were 0% (P > 0.10). The testosterone response rates at day 3 (OR = 1.26; 95%CI: 0.51-3.09; P = 0.62) and the incidence of PSA failure (OR = 0.70; 95%CI: 0.42-1.17; P = 0.18) in the degarelix 240/80 mg were similar to degarelix 240/160 mg (Figure 4).

Other outcomes: There were no differences between the two groups in the median rate of change from baseline levels in PSA up to day 14 (63.24% *vs* 63.51%)

Table 2 Methodological quality of included studies

Ref.	Adequate sequence generation	Adequate allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting
Axcrona *et al*[14]	Unclear	Unclear	High risk	Low risk	Low risk
Anderson *et al*[15]	Unclear	Unclear	High risk	Low risk	Low risk
Mason *et al*[16]	Unclear	Unclear	High risk	Low risk	Low risk
Klotz *et al*[11]	Validated computer program	Low risk	High risk	Low risk	Low risk
Ozono *et al*[10]	Central allocation	Low risk	High risk	Low risk	Low risk
Van Poppel *et al*[12]	Unclear	Unclear	High risk	Low risk	Low risk

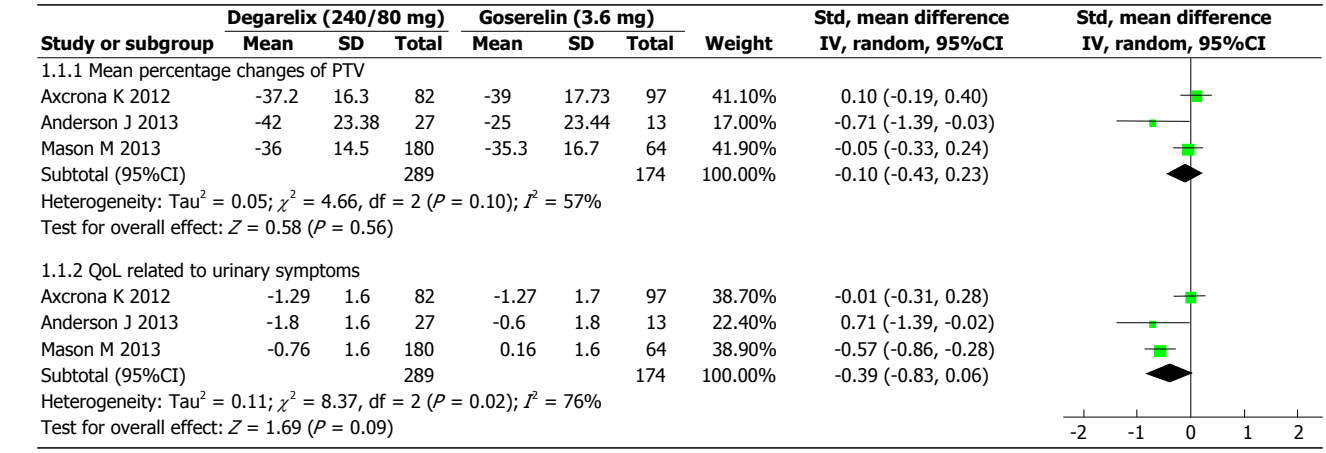

Figure 2 The effects of degarelix (240/80 mg) and goserelin (3.6 mg) on mean percentage changes of total prostate volume and quality of life related to urinary symptoms within included studies. QoL: Quality of life.

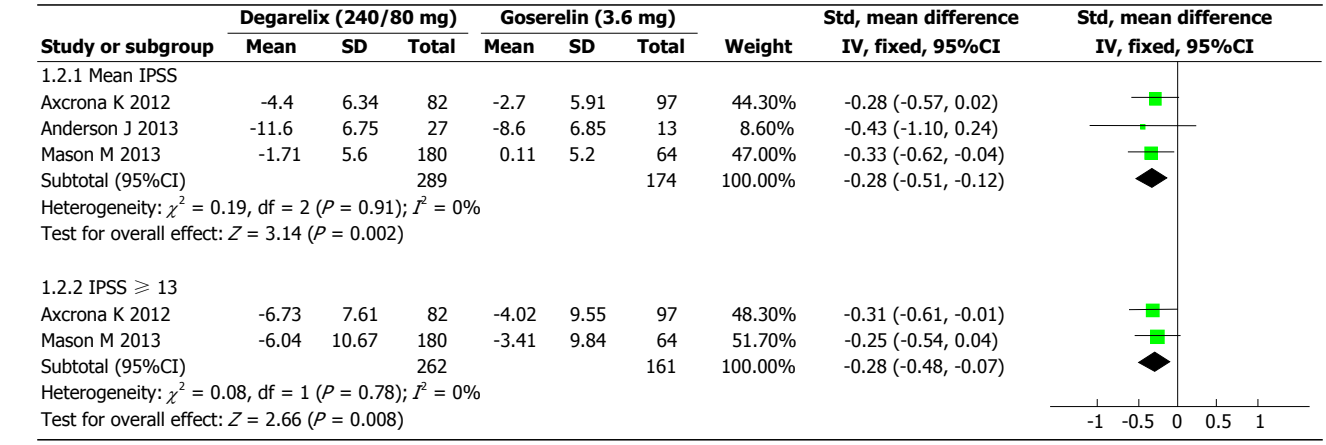

Figure 3 The effects of degarelix (240/80 mg) and goserelin (3.6 mg) on mean International Prostate Symptom Score and International Prostate Symptom Score ⩾ 13 within included studies. IPSS: International Prostate Symptom Score.

and day 28 (82.57% *vs* 81.26%), or in the median reduction in LH at day 1 (85.00% *vs* 84.15%) and at the end of treatment (93.96% *vs* 93.95%). The median reduction in FSH at the end compared with baseline (86.03% *vs* 85.42%).

AEs of degarelix

The AEs associated with the treatment regimens are presented in Table 3. The incidences of AEs due to treatment in patients treated with degarelix 240/80 mg were lower than those treated with goserelin 3.6 mg (OR = 0.62; 95%CI: 0.40-0.95; *P* = 0.03), and were similar in those treated with leuprolide 7.5 mg (OR = 1.07; 95%CI: 0.67-1.71; *P* = 0.78) and degarelix 240/160 mg (OR = 0.80; 95%CI: 0.53-1.2; *P* = 0.29). The incidences of injection site reactions were higher in the degarelix 240/80 mg group than within the goserelin 3.6 mg (OR = 33.08; 95%CI: 15.01-72.93; *P* < 0.00001) and leuprolide 7.5 mg groups (OR = 108.96; 95%CI: 14.96-793.44; *P* < 0.00001). The incidence of injection site reaction were slightly fewer in the degarelix 240/80 mg group than 240/160 mg group (OR = 0.81; 95%CI:

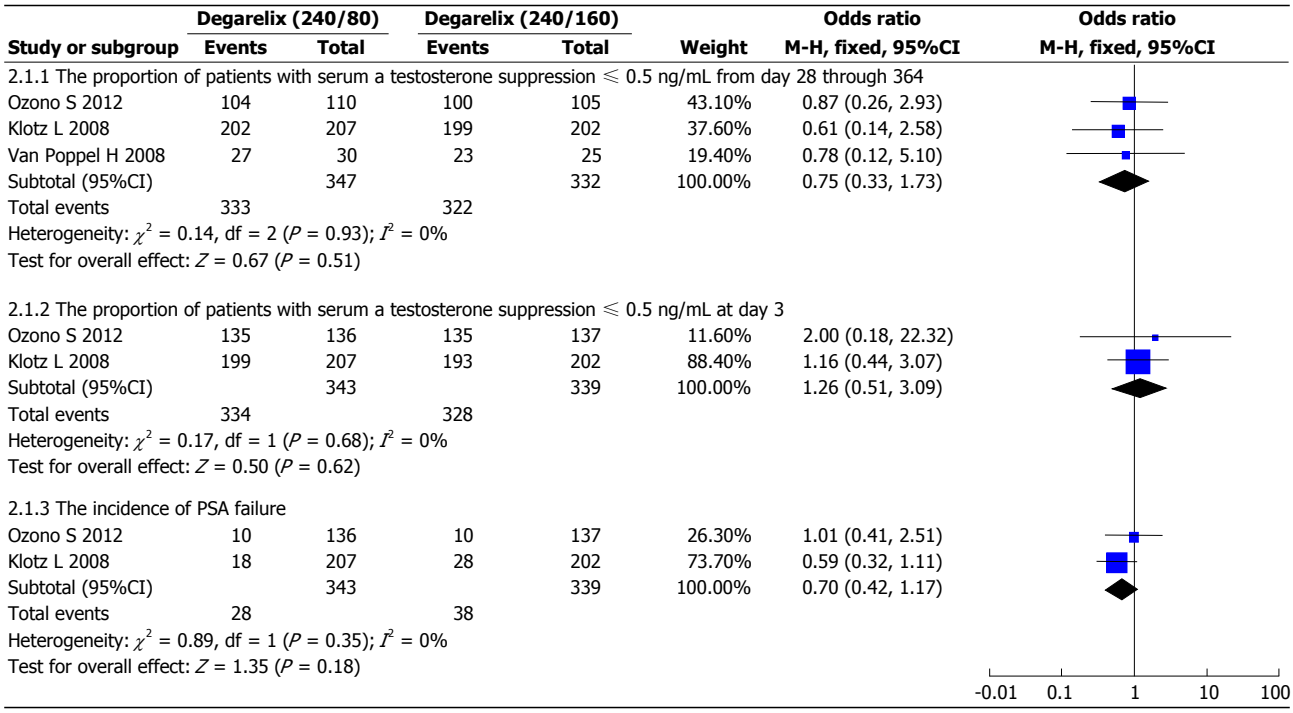

Figure 4 The effect of degarelix (240/80 mg *vs* 240/160 mg) on serum testosterone and prostate-specific antigen within included studies. PSA: Prostate-specific antigen.

0.60-1.09; *P* = 0.16).

DISCUSSION

Summary of key findings: The present study conducted a comprehensive systematic review and meta-analysis to assess the effectiveness of a degarelix 240/80 mg regimen for the treatment of PCa. The results of the systematic review and meta-analysis show that, compared with goserelin 3.6 mg, treatment with degarelix 240/80 mg resulted in a similar decrease in TPV and QoL related to urinary symptoms; and that treatment with degarelix 240/80 mg was preferential in term of the decreasing IPSS scores and reducing treatment-emergent AEs. Our findings were similar to the pooled analysis of individual patient data of degarelix *vs* luteinising hormone releasing hormone agonists by Klotz *et al*[9]. In addition, treatment with degarelix 240/80 mg was not inferior to leuprolide 7.5 mg at maintaining low testosterone levels over a 1-year treatment period. Furthermore degarelix induced testosterone and PSA suppression significantly faster than leuprolide[11]. Both degarelix dosage regimens (240/80 mg and 240/160 mg) maintained castrate levels of testosterone; however, the testosterone suppression was not statistically different between doses. The degarelix 240/80 mg regimen had slightly fewer incidences of treatment-emergent AEs and injection site reactions within PCa patients, but more patients reported with hot flush, weight increase, and UTIs than within those receiving 240/160 mg degarelix.

Strengths and limitations

This is the first systematic review and meta-analysis to comprehensively and systematically compare the clinical effectiveness and safety of degarelix *vs* GnRH agonists (goserelin and leuprolide) for treating PCa, and to decide the best dosage regimen for degarelix treatment. However, there were some limitations. Firstly, though we performed a systematic literature search of common databases and other sources, only 6 RCTs were identified and published in English, which could lead to a publication bias. Secondly, although degarelix has already been widely used as first-line therapy for PCa in the United States, European Union, and Japan[4], evidence in the form of RCTs towards its impact remain limited. Therefore, only a small number of studies could have been included in our review. Thirdly, 4 of the 6 RCTs included in our study failed to report on sequence generation and allocation concealment, and furthermore, were all open-label trials, which might have resulted in an overestimation of the effect[17]. Fourthly, only two dosage regimens of degarelix (240/80 mg and 240/160 mg) were compared for the treatment of PCa. Other dosage regimens (200/80 mg, 200/120 mg, and 200/160 mg) may be superior, and therefore more studies are needed to confirm. Finally, due to the data limitation of included studies, we could not do a meta-analysis on the survival, and we still don't know the influences of degarelix on 3-year, 5-year and overall survival, while these data are important in cancer.

Clinical implications:

Our meta-analysis showed that a degarelix 240/160 mg regimen was more effective and had fewer AEs than the conventional 240/80 mg regimen although 240/80 mg regimen approved by the FDA and EMA. Furthermore,

Table 3 Pooled adverse events for degarelix (240/80 mg) relative to goserelin (3.6 mg), leuprolide (7.5 mg), and degarelix (240/160 mg)

AEs	Degarelix (240/80 mg) *vs* goserelin (3.6 mg)				Degarelix (240/80 mg) *vs* leuprolide (7.5 mg)				Degarelix (240/80 mg) *vs* degarelix (240/160 mg)			
	Stusies (*n*)	Heterogeneity	OR (95%CI)	*P*-value	Studies (*n*)	Heterogeneity	OR (95%CI)	*P*-value	Studies (*n*)	Heterogeneity	OR (95%CI)	*P*-value
Treatment-emergent AEs	3	$I^2 = 0\%$, $P = 0.64$	0.62 (0.40, 0.95)	0.03	1	Not applicable	1.07 (0.67, 1.71)	0.78	3	$I^2 = 0\%$, $P = 0.97$	0.80 (0.53, 1.2)	0.29
Injection site reactions	3	$I^2 = 0\%$, $P = 0.79$	33.08 (15.01, 72.93)	< 0.00001	1	Not applicable	108.96 (14.96, 793.44)	< 0.00001	3	$I^2 = 44\%$, $P = 0.17$	0.81 (0.60, 1.09)	0.16
Hot flush	3	$I^2 = 0\%$, $P = 0.59$	0.80 (0.50, 1.28)	0.35	1	Not applicable	1.26 (0.80, 2.00)	0.32	3	$I^2 = 11\%$, $P = 0.32$	1.23 (0.89, 1.70)	0.22
Weight increase	-	-	-	-	1	Not applicable	0.70 (0.37, 1.34)	0.28	3	$I^2 = 17\%$, $P = 0.30$	1.13 (0.72, 1.76)	0.6
Hypertension	-	-	-	-	1	Not applicable	1.48 (0.59, 3.71)	0.4	2	$I^2 = 0\%$, $P = 0.88$	0.79 (0.44, 1.42)	0.44
Constipation	-	-	-	-	1	Not applicable	0.57 (0.20, 1.60)	0.29	2	$I^2 = 0\%$, $P = 0.45$	0.40 (0.19, 0.84)	0.02
UTI	1	Not applicable	0.08 (0.00-1.88)	0.12	1	Not applicable	0.52 (0.23, 1.15)	0.1	2	$I^2 = 0\%$, $P = 0.45$	3.05 (0.97, 9.61)	0.06
Incidence of PSA recurrence	-	-	-	-	1	Not applicable	0.56 (0.29, 1.09)	0.09	-	-	-	-
Incidence of death	-	-	-	-	1	Not applicable	0.53 (0.17, 1.60)	0.26	-	-	-	-

AEs: Adverse events; PSA: Prostate-specific antigen; OR: Odds ratios.

degarelix was statistically superior to goserelin in decreasing IPSS scores and treatment-emergent AEs, and suppressed testosterone and PSA levels significantly faster than leuprolide. Degarelix is therefore a useful option for the treatment of PCa.

Further direction

Based on the failure of the included studies to report on their methods of randomization and use of blinding, future RCTs should be rigorously designed to ensure such methodology is addressed in future, thereby improving upon the quality of evidence for the use of degarelix in the treatment of PCa. A meta-analysis of dosage-funding and cost-effectiveness studies is needed to confirm the best dosage regimens from an economic point of view. For editors, instructions to authors of meta-analyses should require the disclosure of related item and the CONSORT checklist[18].

COMMENTS

Background

Prostate cancer is one of the most common malignant neoplasm in men. The incidence of prostate cancer and related mortality rates are increasing in many developing countries. Prostate cancer is hormone-sensitive and is the most common initial treatment regime for prostate cancer is androgen deprivation therapy (ADT). Gonadotropin-releasing hormone (GnRH) agonists and antagonists have been approved for ADT in treating advanced prostate cancer. However, degarelix has demonstrated a significantly superior progression-free survival and overall survival rates related to GnRH agonists in a recent pooled individual patient data analysis.

Research frontiers

The conventional monthly degarelix regimen of 240/80 mg (initial dosage/maintenance dosage) has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating advanced prostate cancer. However, present results of phase Ⅱ and Ⅲ studies were inconsistent.

Innovations and breakthroughs

The results of phase Ⅱ and Ⅲ studies show that the efficacy and safety of the 240/80 mg and 240/160 mg degarelix regimens are not markedly different. However, the dosage-funding study by Van Poppel *et al* suggested a regimen of dosage 240 mg and 160 mg is preferred. This is the first systematic review and meta-analysis to comprehensively and systematically compare the clinical effectiveness and safety of degarelix *vs* GnRH agonists (goserelin and leuprolide) for treating prostate cancer, and to decide the best dosage regimen for degarelix treatment.

Applications

This meta-analysis showed that a degarelix 240/160 mg regimen was more effective and had fewer adverse events than the conventional 240/80 mg regimen although 240/80 mg regimen approved by the FDA and EMA. Furthermore, degarelix

was statistically superior to goserelin in decreasing International Prostate Symptom Scores and treatment-emergent adverse events, and suppressed testosterone and prostate-specific antigen levels significantly faster than leuprolide.

Terminology

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. Meta-analysis is the use of statistical methods to summarize the results of independent studies. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review.

Peer-review

It is a well written analysis of the existing evidence regarding degarelix in prostate cancer.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Moore MA**, Ariyaratne Y, Badar F, Bhurgri Y, Datta K, Mathew A, Gangadharan P, Nandakumar A, Pradhananga KK, Talukder MH, Yeole BB, Sobue T. Cancer epidemiology in South Asia - past, present and future. *Asian Pac J Cancer Prev* 2010; **11** Suppl 2: 49-66 [PMID: 20553068]

3 **Kang DI**, Chung JI, Ha HK, Min K, Yoon J, Kim W, Seo WI, Kang Pm, Jung SJ, Kim IY. Korean prostate cancer patients have worse disease characteristics than their American counterparts. *Asian Pac J Cancer Prev* 2013; **14**: 6913-6917 [PMID: 24377625 DOI: 10.7314/APJCP.2013.14.11.6913]

4 **Carter NJ**, Keam SJ. Degarelix: a review of its use in patients with prostate cancer. *Drugs* 2014; **74**: 699-712 [PMID: 24756432 DOI: 10.1007/s40265-014-0211-y]

5 **Zhou ZR**, Liu SX, Zhang TS, Xia J, Li B. Abiraterone for treatment of metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2014; **15**: 1313-1320 [PMID: 24606458 DOI: 10.7314/APJCP.2014.15.3.1313]

6 **Boccon-Gibod L**, Albers P, Morote J, van Poppel H, de la Rosette J, Villers A, Malmberg A, Neijber A, Montorsi F. Degarelix as an intermittent androgen deprivation therapy for one or more treatment cycles in patients with prostate cancer. *Eur Urol* 2014; **66**: 655-663 [PMID: 24954791 DOI: 10.1016/j.eururo.2014.05.037]

7 **Mottet N**, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Schmid HP, Van der Kwast T, Wiegel T, Zattoni F, Heidenreich A. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2011; **59**: 572-583 [PMID: 21315502 DOI: 10.1016/j.eururo.2011.01.025]

8 **Van Poppel H**, Klotz L. Gonadotropin-releasing hormone: an update review of the antagonists versus agonists. *Int J Urol* 2012; **19**: 594-601 [PMID: 22416801 DOI: 10.1111/j.1442-2042.2012.02997.x]

9 **Klotz L**, Miller K, Crawford ED, Shore N, Tombal B, Karup C, Malmberg A, Persson BE. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol* 2014; **66**: 1101-1108 [PMID: 24440304 DOI: 10.1016/j.eururo.2013.12.063]

10 **Ozono S**, Ueda T, Hoshi S, Yamaguchi A, Maeda H, Fukuyama Y, Takeda K, Ohashi Y, Tsukamoto T, Naito S, Akaza H. The efficacy and safety of degarelix, a GnRH antagonist: a 12-month, multicentre, randomized, maintenance dose-finding phase II study in Japanese patients with prostate cancer. *Jpn J Clin Oncol* 2012; **42**: 477-484 [PMID: 22457321 DOI: 10.1093/jjco/hys035]

11 **Klotz L**, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, Jensen JK, Olesen TK, Schröder FH. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008; **102**: 1531-1538 [PMID: 19035858 DOI: 10.1111/j.1464-410X.2008.08183.x]

12 **Van Poppel H**, Tombal B, de la Rosette JJ, Persson BE, Jensen JK, Kold Olesen T. Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker--results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. *Eur Urol* 2008; **54**: 805-813 [PMID: 18538469 DOI: 10.1016/j.eururo.2008.04.065]

13 **Higgins J**, Green SE. Cochrance Handbook for Systematic Reviews of Interventions Version 5.1.0 [EB/OL]. The Cochrane Collaboration, 2011

14 **Axcrona K**, Aaltomaa S, da Silva CM, Ozen H, Damber JE, Tankó LB, Colli E, Klarskov P. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. *BJU Int* 2012; **110**: 1721-1728 [PMID: 22500884 DOI: 10.1111/j.1464-410X.2012.11107.x]

15 **Anderson J**, Al-Ali G, Wirth M, Gual JB, Gomez Veiga F, Colli E, van der Meulen E, Persson BE. Degarelix versus goserelin (+ antiandrogen flare protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: results from a phase IIIb study (NCT00831233). *Urol Int* 2013; **90**: 321-328 [PMID: 23258223 DOI: 10.1159/000345423]

16 **Mason M**, Maldonado Pijoan X, Steidle C, Guerif S, Wiegel T, van der Meulen E, Bergqvist PB, Khoo V. Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: a randomised non-inferiority trial of degarelix versus goserelin plus bicalutamide. *Clin Oncol* (R Coll Radiol) 2013; **25**: 190-196 [PMID: 23257248 DOI: 10.1016/j.clon.2012.09.010]

17 **Di BS**, Wei KP, Tian JH, Xiao XJ, Li Y, Zhang XH, Yu Q, Yang KH, Ge L, Huang WH, Zhang FW. Effectiveness and safety of pemetrexed versus docetaxel as a treatment for advanced non-small cell lung cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2014; **15**: 3419-3424 [PMID: 24870732 DOI: 10.7314/APJCP.2014.15.8.3419]

18 **Wang JC**, Tian JH, Ge L, Gan YH, Yang KH. Which is the best Chinese herb injection based on the FOLFOX regimen for gastric cancer? A network meta- analysis of randomized controlled trials. *Asian Pac J Cancer Prev* 2014; **15**: 4795-4800 [PMID: 24998543 DOI: 10.7314/APJCP.2014.15.12.4795]

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META-ANALYSIS

Antibiotics for eradicating meningococcal carriages: Network meta-analysis and investigation of evidence inconsistency

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Author contributions: Song F had the initial idea; Abdelhamid AS and Song F extracted data from the included trials; Song F conducted data analyses; Abdelhamid AS, Loke YK and Song F investigated causes of inconsistencies, and drafted the manuscript; Abubakar I provided clinical advice on the interpretation of results and critically commented on the manuscript; all authors approved the manuscript.

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Abstract

AIM

To compare different antibiotics for eradicating the carriage of *Neisseria meningitidis* (*N. meningitidis*), and to investigate heterogeneity and evidence inconsistency.

METHODS

From a search of PubMed and published systematic reviews, we identified 23 trials evaluating 15 antibiotics that could be connected in a trial network. The outcome of interest is the eradication of *N. meningitidis*. We used WinBUGS to conduct random-effects, mixed treatment comparisons. Heterogeneity and evidence inconsistency was investigated by meta-regression modelling and examining characteristics of trial participants and interventions evaluated.

RESULTS

Rifampin, ciprofloxacin, minocycline, ceftriaxone, and azythromycin were statistically significantly ($P < 0.05$) more effective than placebo. The probability of being the best was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and below 1% for the remaining regimens. Significant inconsistency between the direct and indirect estimates was observed for the comparison of rifampin and ciprofloxacin ($P < 0.01$), which may be

caused by different types of carriers and different doses of ciprofloxacin.

CONCLUSION

A range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the other two antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines.

Key words: Chemoprophylaxis; Antibiotics; *Nersseria meningitidis*; Meningococcal infection; Network meta-analysis

Core tip: This network meta-analysis found that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages. A combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Careful investigation of significant inconsistency between direct and indirect comparison of rifampin and ciprofloxacin found that it was mainly caused by different types of carriers (persistent or any) and the varying doses of ciprofloxacin in the included trials. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

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INTRODUCTION

Neisseria meningitidis (*N. meningitidis*), a Gram-negative bacterium, is a normal inhabitant of the human pharynx. Transmission from person to person happens by droplets from the upper respiratory tract causing meningococcal disease; the severest forms of which are meningitis and septicaemia[1]. Meningococcal disease occurs usually sporadically or in small clusters all over the world as in the African "meningitis belt", from Ethiopia to Senegal, and also in overcrowded places or wherever large population movements exist[2].

Prevalence of meningococcal carriage varies greatly, from 8% to 25% in random samples of healthy individuals, and as high as 36% to 71% in military recruits, and shows a massive increase in overcrowded places[1]. Current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases irrespective of vaccination status[3-6]. The evidence behind these recommendations were mainly from published systematic reviews[7,8]. However, there is no definite evidence from the available direct comparison trials, as to which antibiotic is more effective in preventing secondary meningococcal disease cases[9].

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been developed to compare different treatment options[10-13]. Because of limited evidence from direct comparison trials, we conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *N. meningitidis*. We also reported the methodological experience obtained from this work for appropriately investigating causes of evidence inconsistencies in network meta-analysis.

MATERIALS AND METHODS

Study eligibility and identification

We included randomised controlled trials that evaluated effects of antimicrobial interventions for the prevention of meningococcal infections. Eligible studies were selected according to the following criteria: (1) it was a randomised controlled study; (2) included participants who exposed to patients with meningococcal disease or *N. meningitidis* carriers; (3) evaluated chemoprophylaxis interventions using any antibiotic regimens; and (4) reported data on eradication of meningococcal carriage. We checked references of previous systematic reviews and conducted additional literature search to identify relevant studies for this meta-analysis. Two recently published high quality systematic reviews (with pairwise meta-analysis only) were identified, in which the literature searches were updated or conducted in June 2013[7] and in December 2013[8] respectively. We assessed the eligibility of studies included in these two reviews. To identify additional eligible studies possibly published after theses systematic reviews, one reviewer (Song F) conducted a search of PubMed in April 2016. The PubMed search used the following key words: "meningococcal" or "meningitis" combined with "chemoprevent*" or "chemoprophyl*" or antibiotic*" or antimicrobial*". In addition, the search was limited to "clinical trial" and published in the last 5 years. However, all relevant studies in the current meta-analysis could be identified from existing systematic reviews, and no new eligible studies were identified from the search of PubMed. Eventually, we included 23 trials[14-35], in which 15 different antibiotics (or combinations of antibiotics) could be connected in a network of trials (Figure 1).

Data extraction

The outcome of interest in this network meta-analysis is failure to eradicate meningococcal carriage up to one week, although only the 2-wk outcome was reported in one trial[14]. From the included studies, two independent reviewers (Asmaa S Abdelhamid and Fujian Song) extracted the following data: Antibiotics evaluated, the number of carriers, the number of carriers with failed eradication at one week after antibiotic prophylaxis, study population, carrier status, reported serogroup, susceptibility of meningococci to antibiotics, study design, adequate or inadequate allocation concealment, and open or blinded. Disagreements between the two reviewers were resolved by discussion.

Methods for mixed treatment comparison

In contrast to within-trial direct comparisons, adjusted indirect comparison is a cross-trial comparison of different treatments, based on a common treatment (for example, placebo), so that the advantage of within-trial randomisation could be partially preserved[10]. Mixed treatment comparison refers to a combination of evidence from direct comparison trials and evidence based on indirect comparisons[12]. The validity of indirect and mixed treatment comparison depends on whether some basic assumptions could be fulfilled. The basic assumptions include homogeneity assumption for conventional pair-wise meta-analysis, trial similarity assumption for adjusted indirect comparison, and consistency assumption for combining direct and indirect evidence[36]. Among these basic assumptions, heterogeneity in conventional meta-analysis and inconsistency between direct and indirect evidence can be quantitatively assessed.

Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, United Kingdom) were used to conduct the random-effects, mixed treatment comparisons based on consistency assumption[37]. The WinBUGS code for Bayesian analysis is available from a report by Dias *et al*[37,38]. We used non-informative or vague priors, and obtained results by 200000 iterations after a burn-in of 100000.

Investigating heterogeneity and causes of inconsistency

When different antibiotics could be compared both directly and indirectly, we calculated the inconsistency (Δ) between the direct and indirect evidence by the following:

$$\Delta = d_{CB} - d'_{CB}$$

$$se(\Delta) = \sqrt{Var(d_{CB}) + Var(d'_{CB})}$$

Where d_{CB} and d'_{CB} are the treatment effects (*e.g.*, log odds ratio) by direct and indirect comparison of treatment *C* and *B*; $se(\Delta)$ is the standard error of the estimated inconsistency; $Var(d_{CB})$ and $Var(d'_{CB})$ are estimated variances of the treatments effects.

We used a statistical model suggested by Cooper *et al*[39] to explore treatment by covariate interactions in the network meta-analysis. It estimates a regression coefficient by assuming a single interaction term for the relative effects of all the treatments *vs* the reference treatment (*i.e.*, placebo)[38]. The effects of the following study-level covariates were investigated: Persistent carriers *vs* any carriers, household contacts *vs* other carriers, cluster/quasi randomised controlled trials *vs* randomised trials, adequate *vs* inadequate sequence generation, and open *vs* blinded design.

We also conducted narrative investigation of causes of inconsistency, which was focused on detailed comparison of rifampin and ciprofloxacin (reasons for this will be provided later). The assessment of clinical diversity and similarity among different sets of trials is a process of identifying possible effect modifiers, which was conducted by answering the following two questions[40]. First, we examined whether there were noticeable differences in study characteristics between different sets of trials. Then, we considered whether any of the observed differences in study characteristics between trials may have modified the relative treatment effects. In this study, we examined individual trials for effect modifiers with special attention to carriage status, dose of antibiotic used and length of intervention.

There were 14 trials that compared antibiotics and placebo. Using data from these placebo-controlled trials, we produced a funnel plot to investigate risk of publication bias. Asymmetry of the funnel plot was statistically tested using Harbord's test for small-study effects[41]. All statistical analyses were conducted and checked by the corresponding author (Fujian Song) who has training and experience in statistical methods.

RESULTS

The main characteristics of the 23 trials are presented in Table 1, and data used in network meta-analyses are shown in Table 2. There are 20 two-arm trials, one three-arm trial, and two four-arm trials. The 15 antibiotics evaluated in these trials are: Placebo, rifampin, ciprofloxacin, minocycline, minocycline plus rifampin, penicillin, ampicillin, ceftriaxone, sulphadiazine, sulphadimidine, azythromycin, spectinomycin, cephalexin, "Sch29482", and coumermycin A1 (Figure 1).

Carriers were mainly from household contacts of cases (six trials), military recruits (seven trials), and students or young people (six trials). Six trials recruited heavy or persistent carriers (defined as two or more sequential positive cultures before antibiotic prophylaxis). The test of susceptibility to antibiotics was done in most of the studies. The sequence generation was inadequate or unclear in 11 trials. Blinding was performed in 12 trials, and allocation concealment was adequate in only three trials (Table 1).

There were five cluster randomised trials. We could not find empirical data on intra-cluster correlation coefficient (ICC) for the included cluster randomised trials, and therefore estimated the effective sample

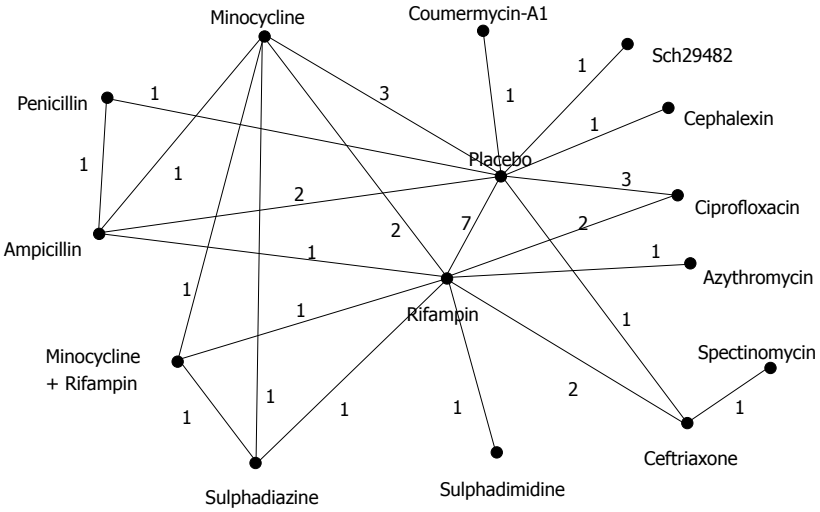

Figure 1 Network of comparisons antibiotics for preventing meningococcal infections. The lines that connect antibiotics refer the direct comparison of two antibiotics. The number beside a line is the number of trials that directly compared the two antibiotics lined by the line.

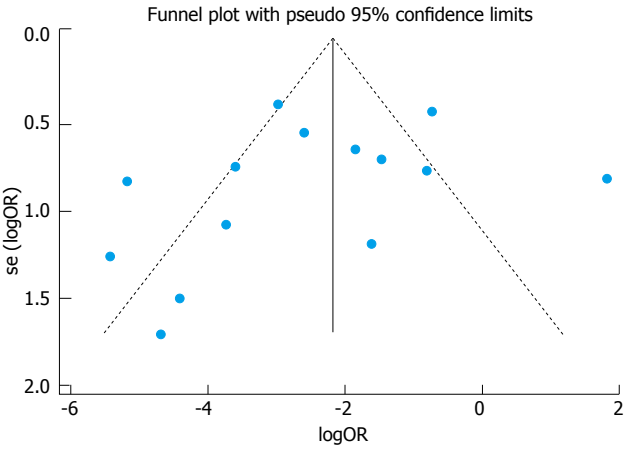

Figure 2 Funnel plot - estimated effects (log odds ratio) of antibiotics in placebo-controlled studies. Funnel plot asymmetry was not statistically significant (Harbord's test for small study effects $P = 0.600$).

sizes by assuming an ICC of 0.05[42].

Funnel plot using data from 14 placebo-controlled trials is shown in Figure 2. The funnel plot was not statistically significantly asymmetric ($P = 0.610$), indicating no concern about risk of small-study effects.

Comparison of antibiotics

The results of the network meta-analysis are shown in Table 3. Rifampin, ciprofloxacin, minocycline, ceftriaxone and azythromycin were significantly ($P < 0.05$) more effective than placebo. The probability of being the most efficacious was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and less than 1% for the remaining antibiotics. According to evidence from the full network of trials, the combination of rifampin and minocycline was the most efficacious intervention, and ceftriaxone the second (Table 3).

The covariate effects in the network meta-analysis are shown in Table 4. Trials with persistent carriers or household contacts of cases reported significantly greater treatment effects as compared with trials of any carriers or non-household contacts of cases, while the remaining regression coefficients were not statistically significant. When the effect of persistent carrier was incorporated into the network meta-analysis, the between-study variation ($\tau = 0.434$) was much reduced as compared with the between-study variation without significant covariate adjustment ($\tau > 0.937$). Therefore, type of carriers (persistent *vs* any) may be an effect modifier[39]. However, the between-study variation was not reduced when the effect of household contacts was included in the analysis ($\tau = 0.975$).

Inconsistencies in the network meta-analysis

There is sufficient data for both direct and indirect comparisons of four pairs of antibiotics (Table 5), and the estimated inconsistencies between the direct and indirect estimates are shown in Figure 3. A statistically significant inconsistency was observed for the comparison of rifampin and ciprofloxacin. The indirect comparison based on 21 trials found that rifampin was significantly better than ciprofloxacin (OR = 0.09, 95%CI: 0.017-0.40 for failure to eradicate). In contrast, the pooling of two direct comparison trials suggested that rifampin therapy was less effective than ciprofloxacin, with a greater likelihood (non-statistically significant) of failure to eradicate (OR = 2.51, 95%CI: 0.36-15.64).

Our further investigation of causes of inconsistency was therefore focused on the comparison of rifampin and ciprofloxacin. These are also the antibiotics recommended in the current clinical guidelines. The inconsistency investigation was using data from two direct comparison trials[16,29], six placebo-controlled trials of rifampin[15,17,19,20,26,28] and three placebo-controlled trials of ciprofloxacin[24,31,33]. Figure 4 shows the results of the individual trials, with the overall estimates of direct and indirect comparisons.

While placebo controlled trials of rifampin included mostly any carriers, three placebo controlled trials of ciprofloxacin included heavy or persistent carriers (Table 1). Consequently, as shown in Figure 5, the proportion of patients with failed eradication in the placebo arm

Table 1 Main characteristics of studies included in network meta-analysis

Ref.	Antibiotics	Country and population	Carrier status	Serogroups and susceptibility	Study design	Sequence generation	Allocation concealment	Blinding
Blakebrough *et al*[14]	Rifampin: 4 × 75 mg for 0-2 yr, 4 × 150 mg for 2-4 yr, 4 × 300 mg for 5-14 yr, 4 × 600 mg for > 15 yr (bid, 2 d) Sulphadimidine: 4 × 250 mg for 0-4 yr, 4 × 500 mg for 5-14 yr, 4 × 1 g for > 15 yr (bid, 2 d)	Nigeria Household contacts	Any carriers	Group A Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Borgoño *et al*[15]	Rifampin: 2 × 10 mg/kg Placebo	Chile Children	Any carriers	Group unknown Susceptibility not tested	RCT	Unclear	Unclear	Double-blind
Cuevas *et al*[16]	Rifampin: 4 × 600 mg for > 18 yr, 4 × 20 mg/kg for 2-18 yr (bid, 2 d) Ciprofloxacin: 1 × 750 mg for > 18 yr, 1 × 15 mg/kg for 2-18 yr	Malawi Household contacts	Any carriers	Group A: 51% (unknown 49%) Susceptibility tested	Cluster RCT	Unclear	Unclear	Open
Deal *et al*[17]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Healthy students	Heavy/ Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deal *et al*[18]	Cephalexin: 12 × 500 mg (tid, 4 d) Placebo	United States Students	Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deviatkina *et al*[19]	Rifampin: 4 × 300 mg (4 d) Placebo	Russia Unclear	Unknown	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Open
Devine *et al*[20]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Army recruits	Any carriers	Group Y: 79% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[21]	Coumermycin A1: 14 × 50 mg (bid, 7 d) Placebo	United States Army recruits	Any carriers	Group unknown Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 1 × 200 mg + 9 × 100 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group Y: 63% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 4 × 200 mg (bid, 2 d) No antibiotic	United States Army recruits	Any carriers	Group Y: Most Susceptibility tested	RCT	Adequate	Unclear	Open
Dowd *et al*[23]	Ampicillin: 30 × 500 mg (tid, 10 d) Penicillin: 30 × 462 mg (tid, 10 d) Placebo	United States Amy recruits	Any carriers	Group B and sulfadiazine-resistant	RCT	Unclear	Unclear	Double-blind
Dworzack *et al*[24]	Ciprofloxacin: 1 × 750 mg Placebo	United States Young adults	Persistent (3 positive cultures)	Group B: 41%, Z: 33% Susceptibility tested	RCT	Unclear	Unclear	Double-blind
Girgis *et al*[25]	Rifampin: 4 × 600 mg (bid, 2 d) Azithromycin: 1 × 500 mg	Egypt Nursing students	Any carriers	Group A: 37%; B: 33% Susceptibility tested	RCT	Adequate	Unclear	Open
Guttler *et al*[26]	Rifampin: 5 × 600 mg (5 d) Minocycline 10 × 100 mg (bid, 5 d) Ampicillin 10 × 500 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group B or C: 31% (non-groupable 67%) Susceptibility tested	Cluster RCT	Adequate	Unclear	Open
Judson *et al*[27]	Ceftriaxone: im 1 × 125 mg Spectinomycin: im 1 × 2 g	United States Patients with gonorrhoea	Any carriers	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Outcome assessment blinded

Kaiser *et al*[28]	Rifampin: 4 × 600 mg for weight ⩾ 66 lb, or 4 × 300 mg for weight < 66 lb (4 d) Placebo	United States Household contacts	Any carriers	Group C: 35% Susceptibility tested	RCT	Adequate	Unclear	Open
Kaya *et al*[29]	Rifampin: 4 × 600 mg (bid, 2 d) Ciprofloxacin: 1 × 750 mg	Turkey Healthy adults	Any carriers	Group unknown Susceptibility not tested	Quasi RCT	Inadequate	Inadequate	Open
Munford *et al*[30]	Rifampin: 4 × 600 mg (bid, 2 d) Minocycline: 1 × 200 mg + 5 × 100 mg (bid, 3 d) Rifampin + Minocycline: as above Sulphadiazine: 4 × 1 g (bid, 2 d)	Brazil Household contacts	Any carriers	Group C: Most Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Pugsley *et al*[32]	Sch29482: 16 × 250 mg (every 6 h for 4 d) Placebo	United States	Persistent carriers (2 positive cultures)	Group Z: 36%; B: 24%	RCT	Adequate	Unclear	Double-blind
Pugsley *et al*[31]	Ciprofloxacin: 10 × 500 mg (bid, 5 d) Placebo	Young men United States	Persistent (2 positive cultures)	Susceptibility tested Group B: 79%	RCT	Adequate	Unclear	Double-blind
Renkonen *et al*[33]	Ciprofloxacin: 4 × 250 mg (bid, 2 d) Placebo	Young adults Finland	Heavy (> 100 colonies per plate)	Susceptibility tested Group B: 45%	RCT	Adequate	Adequate	Double-blind
Schwartz *et al*[34]	Rifampin: 4 × 600 mg or 4 × 10 mg/kg (bid, 2 d)	Army recruits Saudi Arabia	Any carriers	Susceptibility tested Group A	Cluster RCT	Unclear	Unclear	Open
Simmons *et al*[35]	Ceftriaxone: im 1 × 250 mg (or 125 mg for < 15 yr) Rifampin: 4 × 600 mg for adults, 4 × 5 mg/kg for children < 1 mo, and 4 × 10 mg for children > 1 mo (bid, 2 d) Ceftriaxone: im 1 × 250 mg, or 1 × 125 mg for < 12 yr	Household contacts New Zealand Household contacts	Any carriers	Susceptibility tested Group B: 53% Susceptibility tested	RCT	Unclear	Unclear	Open

im: Intramuscular; bid: Twice a day; tid: Three times a day; RCT: Randomized controlled trials.

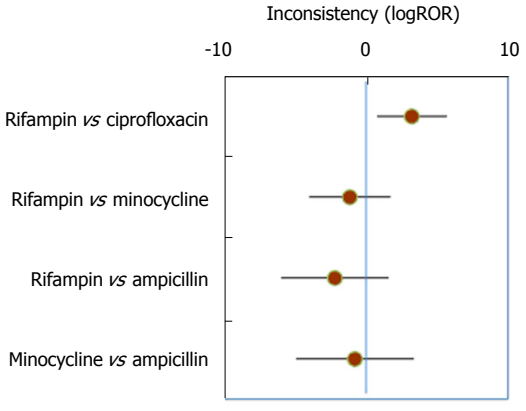

Figure 3 Inconsistencies (and 95%CIs) between direct and indirect estimates for comparisons with closed loops. logROR: 0 indicates no difference between the direct and indirect estimates.

trials of rifampin (83% *vs* 55%). If the absolute results of antibiotic interventions were not influenced by the proportion of participants with persistent carriage, trials that included persistent carriers will show greater relative treatment effects purely because of the high failure rates in the placebo group (Figure 5). Therefore, imbalanced distribution of types of carriers across different sets of trials may invalid the similarity assumption in the network meta-analysis, which raises a question whether the indirect comparison is valid in this case.

In addition, the use of ciprofloxacin in the direct comparison trials[16,29] was different from its use in the placebo-controlled trials of ciprofloxacin[24,31,33]. A single dose of ciprofloxacin was compared with multiple doses of rifampin in the two direct comparison trials, while two of the three placebo-controlled trials of ciprofloxacin compared placebo and multiple doses of ciprofloxacin (Table 1). Therefore, the effect of ciprofloxacin (with multiple doses) in the placebo-controlled trials may be enhanced as compared to the single dose in the two direct comparison trials. The eradication failure in the ciprofloxacin arm at one week was 10.5% in the direct comparison trials, as compare with only 3.0% in the placebo-controlled trials (Figure 5). The different doses of ciprofloxacin used in the direct comparison trials and in the placebo-controlled trials also contributed to the significant inconsistency observed.

DISCUSSION

According to this network meta-analysis, a range of

Table 2 Antibiotics compared and data from the included trials for network meta-analysis

Trial	Regimen	*n*	Failure to eradicate
Guttler *et al*[26]	Placebo	18 (146)	8 (65)
	Rifampin	18 (147)	2 (13)
	Minocycline	18 (147)	1 (12)
	Ampicillin	18 (147)	3 (22)
Munford *et al*[30]	Rifampin	65 (67)	6 (6)
	Sulphadiazine	79 (82)	37 (38)
	Minocycline	56 (58)	6 (6)
	Rifampin + Minocycline	59 (61)	0 (0)
Schwartz *et al*[34]	Rifampin	34 (36)	9 (9)
	Ceftriaxone	65 (68)	2 (2)
Dowd *et al*[23]	Placebo	47	26
	Penicillin	20	9
	Ampicillin	26	8
Borgoño *et al*[15]	Placebo	110	71
	Rifampin	118	10
Deal *et al*[17]	Placebo	15	13
	Rifampin	15	2
Deviatkina *et al*[19]	Placebo	43	10
	Rifampin	46	3
Devine *et al*[20]	Placebo	28	25
	Rifampin	38	7
Kaiser *et al*[28]	Placebo	6	6
	Rifampin	13	1
Dworzack *et al*[24]	Placebo	22	20
	Ciprofloxacin	24	1
Pugsley *et al*[31]	Placebo	21	14
	Ciprofloxacin	21	0
Renkonen *et al*[33]	Placebo	53	46
	Ciprofloxacin	56	2
Deal *et al*[18]	Placebo	15	14
	Cephalexin	15	11
Devine *et al*[22]	Placebo	48	42
	Minocycline	41	14
Devine *et al*[22]	Placebo	29	27
	Minocycline	53	16
Devine *et al*[21]	Placebo	39	28
	Coumermycin A1	33	31
Pugsley *et al*[32]	Placebo	29	26
	Sch29482	29	23
Cuevas *et al*[16]	Rifampin	84 (88)	3 (3)
	Ciprofloxacin	75 (79)	9 (9)
Kaya *et al*[29]	Rifampin	25	1
	Ciprofloxacin	26	2
Girgis *et al*[25]	Rifampin	59	3
	Azythromycin	60	4
Simmons *et al*[35]	Rifampin	82	4
	Ceftriaxone	100	3
Blakebrough *et al*[14]	Rifampin	46 (48)	11 (11)
	Sulphadimidine	33 (34)	33 (34)
Judson *et al*[27]	Ceftriaxone	29	0
	Spectinomycin	9	8

For cluster trials, ICC = 0.05 was assumed for estimating effective sample sizes, and original sample size and events in cluster trials are shown in brackets.

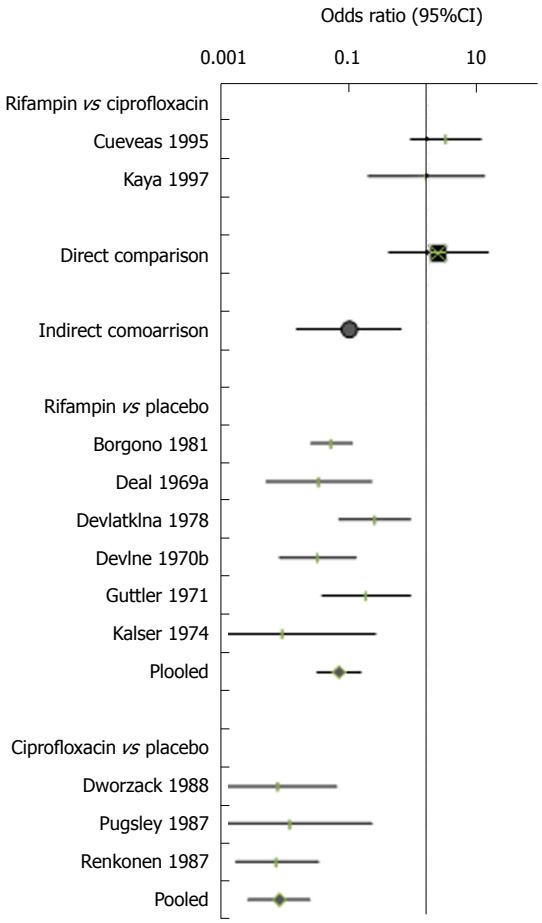

Figure 4 Rifampin *vs* ciprofloxacin for preventing meningococcal infections. The outcome is the failure to eradicate at 1 wk. Pooled direct and indirect estimates were the results of mixed treatment comparison, and other results were from DerSimonian-Laird meta-analyses.

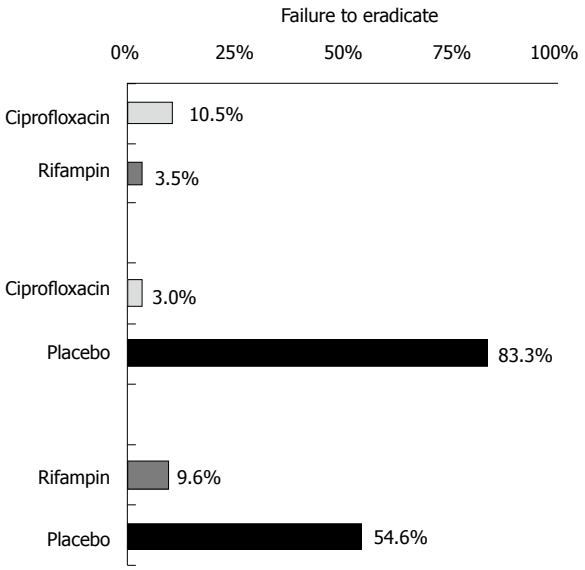

Figure 5 Proportions of failure to eradicate in individual arms of trials for the direct and indirect comparison of rifampin and ciprofloxacin.

antibiotic regimens are effective for preventing meningococcal infections in carriers. The simultaneous analysis of all randomised controlled trials that could be connected in a coherent network provided results that were not available from the conventional pair-wise meta-analysis[43]. The network meta-analysis revealed that a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than the antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines[4-6]. The network

Table 3 Results of network meta-analysis of antibiotics for preventing meningococcal infections (odds ratio of failure to eradicate)

	2 Rifampin	3 Ciprofloxacin	4 Cephalexin	5 Minocycline	6 Ampicillin	7 Penicillin	8 Ceftriaxone	9 Rifampin + minocycline	10 Azythromycin	11 Spectinomycin	12 Coumermycin A1	13 Sch29482	14 Sulphadiazine	15 Sulphadimidine
1 Placebo	0.038[a]	0.020[a]	0.274	0.058[a]	0.267	0.611	0.009[a]	0.004[a]	0.071[a]	5.971	5.524	0.498	0.487	23.17
2 Rifampin		0.53	7.201	1.536	7.028[a]	16.20[a]	0.247	0.098	1.89	156.2[a]	146.2[a]	13.15[a]	12.88[a]	601[a]
3 Ciprofloxacin			13.7	2.911	13.29[a]	30.67[a]	0.467	0.184	3.54	301.0[a]	278.0[a]	24.87[a]	24.4[a]	1174[a]
4 Cephalexin				0.214	0.980	2.26	0.035[a]	0.013[a]	0.262	22.42	20.6	1.826	1.825	91.1[a]
5 Minocycline					4.577	10.52	0.161	0.064	1.212	102.3[a]	95.57[a]	8.53	8.42[a]	396[a]
6 Ampicillin						2.291	0.035[a]	0.014[a]	0.266	22.54	20.85[a]	1.864	1.84	88.6[a]
7 Penicillin							0.015[a]	0.006[a]	0.116	9.808	9.128	0.81	0.8	39.09
8 Ceftriaxone								0.385	7.566	620[a]	597[a]	53.17[a]	52.94[a]	2493[a]
9 Rifampin + minocycline									20.15	1776[a]	1584[a]	140.2[a]	134.3[a]	7088[a]
10 Azythromycin										83.64[a]	78.9[a]	7.03	7	334[a]
11 Spectinomycin											0.924	0.082	0.084	4.032
12 Coumermycin A1												0.089	0.088	4.372
13 Sch29482													0.992	48.75
14 Sulphadiazine														47.14

[a]95%CIs did not contain zero.

meta-analysis also revealed significant inconsistency between direct and indirect estimates for the comparison of rifampin and ciprofloxacin. We investigated causes of the observed inconsistency and found that it was likely due to the following two effect modifiers: Types of carriers (persistent *vs* any), and the varying doses of ciprofloxacin.

The superior efficacy of rifampin and minocycline means it should be considered for areas where there is high degree of resistance to other agents, or in groups of patients where high rates of eradication are considered to be essential. The most efficacious regimen (rifampin and minocycline) was reported to have a significantly increased risk of adverse effects as compared to either drug alone[30]. Headache, dizziness, nausea, or vomiting were specific adverse effects noted more frequently in patients receiving the rifampin-minocycline combination. Nevertheless, patients who consider eradication of carriage to be their top priority may choose to put up with these adverse effects in order to have the best chance of treatment success.

Equally, the effectiveness of single dose intramuscular ceftriaxone, without any need to worry about patient adherence to oral regimens, makes it particularly suitable for patients when there are concerns surrounding the likelihood of the patient being able to regularly take several oral doses as prescribed. For instance, ceftriaxone would be an efficacious option in younger children who have difficulty taking tablets. Moreover, a single dose of ceftriaxone would appear to be less risky option than either ciprofloxacin or rifampin in women who are pregnant or breastfeeding. Use of ceftriaxone in both of these patient groups would be in-line with the United States CDC recommendations[3], and our network meta-analysis now provides the relevant evidence base to support this guidance.

Although the current guidelines in the United Kingdom recommend ciprofloxacin because it can be conveniently used as a single dose regimen, the results of inconsistency investigation indicate that single dose ciprofloxacin may be less effective than either multiple dose ciprofloxacin or rifampin. A regimen of multiple doses of ciprofloxacin seems preferable for persistent carriers (according to evidence from placebo-controlled trials). However, the emergence of ciprofloxacin-resistant *N. meningitidis* should also be taken into consideration[44].

Choice of optimal antibiotic strategy will be inevitably influenced by considering many factors such as cost, convenience, adherence, tolerability and bacterial resistance in a trade-off against the rate of failed eradication. For example, rifampin has been an important antibiotic agent in tuberculosis treatment, and to minimise the risk of bacterial resistance, it is not recommended as a prophylactic agent for household contacts in sub-Saharan Africa[6].

Table 4 Results of covariate effects in network meta-analysis: Regression coefficient and between study variation

Covariate	Regression coefficient, β (95%CI)	Between-study variation (τ)
Persistent carrier (1) *vs* any carriers (0)	-2.904 (-4.695 to -1.186)	0.434
Household (1) *vs* other (0)	-6.178 (-16.79 to -0.069)	0.975
Cluster/quasi RCT (1) *vs* RCT (0)	0.405 (-2.235 to 2.881)	1.082
Sequence generation inadequate (1) *vs* adequate (0)	0.461 (-1.301 to 2.014)	1.025
Open design (1) *vs* blinded (0)	0.055 (-1.877 to 1.662)	1.087

β > 0 indicating that treatment effect is smaller when the covariate exists. RCT: Randomized controlled trial.

Table 5 Results of different methods for four comparisons that provided sufficient trials for both direct and indirect comparisons

	MTC estimate		Direct estimate		Indirect estimate	
Comparison	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)
Rifampin *vs* ciprofloxacin	23	0.52 (0.13, 1.89)	2	2.51 (0.36, 15.64)	21	0.09 (0.017, 0.40)
Rifampin *vs* minocycline	23	1.55 (0.40, 6.07)	2	0.85 (0.11, 5.59)	21	2.27 (0.28, 19.89)
Rifampin *vs* ampicillin	23	6.94 (1.21, 37.53)	1	1.62 (0.09, 29.82)	20	12.23 (1.04, 146.9)
Minocycline *vs* ampicillin	23	4.52 (0.67, 28.30)	1	3.46 (0.16, 91.10)	20	6.50 (0.41, 93.6)

MTC: Mixed treatment comparison based on all data in the network of trials.

Methodological implications

One of the main advantages of network meta-analysis is pooling of all connected trials into a coherent network of evidence. However, a study found that the inconsistency between direct and indirect evidence may be more prevalent than previously observed[45], and it has been generally accepted that causes of inconsistency in network meta-analysis should be carefully investigated[36,46-48]. In the current study, statistical meta-regression analyses found that the type of carriers (persistent *vs* any, and household contacts *vs* other) may be a cause of heterogeneity in the network meta-analysis. However, the usefulness of statistical methods for investigating causes of inconsistency is often limited because of the small number of trials, inadequate reporting of relevant variables, and modelling complexity.

The narrative investigation of causes of inconsistency is difficult for a complex network. The existence of evidence inconsistencies in a network meta-analysis does not mean that the whole network is inconsistent[46]. Therefore, we focused on the investigation of statistically significant inconsistencies. To further simplify the narrative investigation, a sub-network of trials was formed after excluding those that are only remotely connected to the target comparison.

We demonstrated that focused examination of characteristics of trial participants and interventions evaluated may reveal the clinically meaningful causes of inconsistency in network meta-analysis. The detailed examination of trial participants and interventions evaluated is similar to the investigation of heterogeneity in conventional pair-wise meta-analysis. Although the type of carriers (persistent *vs* any) can be identified by both statistical covariate analysis and narrative investigation, the difference in doses of ciprofloxacin as a possible cause of inconsistency could not be investigated by the statistical models we used. However, the narrative investigation mainly relies on subjective judgement, is restricted by available data from published studies, and a good understanding of the topic is required.

Study limitations

In order to include as many studies as possible in the trial network, we focused on eradication failure and did not consider other important outcomes such as adverse effects and new cases of meningococcal disease. Included studies were mostly conducted in 1970s or 1980s, and the most recent study was published in 2000[35]. Therefore, it is a question about whether the results of previous randomised controlled trials are applicable to the present. Although we included only randomised controlled trials, the quality of the included trials was poor, with considerable risk of bias. According to the results of meta-regression analyses (Table 4), the treatment effects were not significantly associated with whether a trial was cluster or quasi randomised, whether the sequence generation was inadequate, and whether it was blinded. In addition, publication and outcome reporting bias was possible. Funnel plot using data from placebo-controlled trials indicated that there was no statistically significant small-study effect.

Conclusion

The network meta-analysis confirms that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the two

recommended antibiotics (ciprofloxacin or rifampin) by the current guidelines. Variation in the type of carriage and dosage regimens of ciprofloxacin may account for the observed inconsistency in the direct and indirect comparisons of rifampin and ciprofloxacin. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

COMMENTS

Background

The current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases of meningococcal meningitis. Because of limited evidence from direct comparison trials, the authors conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *Neisseria meningitidis* (*N. meningitidis*).

Research frontiers

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been widely used to compare different treatment options.

Innovations and breakthroughs

This is the first network meta-analysis to compare the efficacy of competing antibiotics for eradicating the carriage of *N. meningitidis*. Methodological experience obtained from this network meta-analysis was also reported.

Applications

For eradicating meningococcal carriages, a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in all network meta-analysis.

Terminology

Network meta-analysis can be used to combine evidence from direct comparison trials and evidence based on indirect comparisons.

Peer-review

This is a well-performed network meta-analysis regarding the effects of antibiotics for eradicating carriages of *N. meningitidis*. The methodology is clear, the meta-analysis was performed well, the article was well-written, and the limitations of the study have been adequately discussed. The findings of this meta-analysis should be useful for the scientific and clinical community.

REFERENCES

1 **Stephens DS**, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. *Lancet* 2007; **369**: 2196-2210 [PMID: 17604802 DOI: 10.1016/s0140-6736(07)61016-2]

2 **Harrison LH**, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009; **27** Suppl 2: B51-B63 [PMID: 19477562 DOI: 10.1016/j.vaccine.2009.04.063]

3 **ACIP**. Prevention and control of meningococcal disease. Recommendations of the Advisary Committee on Immunization Practice. In: Morbidity and Mortality Weekly Report. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, 2005

4 **ECDC**. Public health management of sporadic cases of invasive meningococcal disease and their contacts. Stockholm: ECDC Guidance Stockholm European Centre for Disease Prevention and Control, 2010

5 **HPA**. Guidance for public health management of meningococcal disease in the UK (Version 01.4-2011). In: London: Health Protection Agency, 2011

6 **WHO**. Meningitis Outbreak Response in Sub-Saharan Africa: WHO Guideline. Geneva: World Health Organization, 2014

7 **Zalmanovici Trestioreanu A**, Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. *Cochrane Database Syst Rev* 2013; **(10)**: CD004785 [PMID: 24163051 DOI: 10.1002/14651858.CD004785.pub5]

8 **Telisinghe L**, Waite TD, Gobin M, Ronveaux O, Fernandez K, Stuart JM, Scholten RJ. Chemoprophylaxis and vaccination in preventing subsequent cases of meningococcal disease in household contacts of a case of meningococcal disease: a systematic review. *Epidemiol Infect* 2015; **143**: 2259-2268 [PMID: 25916733 DOI: 10.1017/s0950268815000849]

9 **Purcell B**, Samuelsson S, Hahné SJ, Ehrhard I, Heuberger S, Camaroni I, Charlett A, Stuart JM. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. *BMJ* 2004; **328**: 1339 [PMID: 15178612 DOI: 10.1136/bmj.328.7452.1339]

10 **Bucher HC**, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; **50**: 683-691 [PMID: 9250266 DOI: 10.1097/MD.0000000000003185]

11 **Higgins JP**, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996; **15**: 2733-2749 [PMID: 8981683 DOI: 10.1002/(SICI)1097-0258(19961230)15]

12 **Lu G**, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23**: 3105-3124 [PMID: 15449338 DOI: 10.1002/sim.1875]

13 **Lumley T**. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002; **21**: 2313-2324 [PMID: 12210616 DOI: 10.1002/sim.1201]

14 **Blakebrough IS**, Gilles HM. The effect of rifampicin on meningococcal carriage in family contacts in northern Nigeria. *J Infect* 1980; **2**: 137-143 [PMID: 6821084 DOI: 10.1016/S0163-4453(80)91159-7]

15 **Borgoño JM**, Rodríguez H, García J, Cánepa I. Efficacy of rifampicin in the treatment of Meningococcus carriers. *Rev Chil Pediatr* 1981; **52**: 146-148 [PMID: 6792661 DOI: 10.4067/S0370-41061981000200007]

16 **Cuevas LE**, Kazembe P, Mughogho GK, Tillotson GS, Hart CA. Eradication of nasopharyngeal carriage of Neisseria meningitidis in children and adults in rural Africa: a comparison of ciprofloxacin and rifampicin. *J Infect Dis* 1995; **171**: 728-731 [PMID: 7876629 DOI: 10.1093/infdis/171.3.728]

17 **Deal WB**, Sanders E. Efficacy of rifampin in treatment of meningococcal carriers. *N Engl J Med* 1969; **281**: 641-645 [PMID: 4980025 DOI: 10.1056/nejm196909182811203]

18 **Deal WB**, Sanders E. Therapeutic trial of cephalexin in meningococcal carriers. *Antimicrob Agents Chemother* (Bethesda) 1969; **9**: 441-444 [PMID: 5396522]

19 **Deviatkina NP**, Demina AA, Orlova EV, Timina VP, Petrova IS. Evaluation of the sanative action of rifampicin on the meningococcal carrier state. *Antibiotiki* 1978; **23**: 794-797 [PMID: 100048]

20 **Devine LF**, Johnson DP, Hagerman CR, Pierce WE, Rhode SL, Peckinpaugh RO. Rifampin. Levels in serum and saliva and effect on the meningococcal carrier state. *JAMA* 1970; **214**: 1055-1059 [PMID: 4990906 DOI: 10.1001/jama.1970.03180060033006]

21 **Devine LF**, Johnson DP, Hagerman CR, Pierce WE, Rhode SL, Peckinpaugh RO. The effect of coumermycin A on the meningococcal carrier state. *Am J Med Sci* 1970; **260**: 165-170 [PMID: 4991431 DOI: 10.1097/00000441-197009000-00004]

22 **Devine LF**, Johnson DP, Hagerman CR, Pierce WE, Rhode SL, Peckinpaugh RO. The effect of minocycline on meningococcal nasopharyngeal carrier state in naval personnel. *Am J Epidemiol* 1971; **93**: 337-345 [PMID: 4997355]

23 **Dowd JM**, Blink D, Miller CH, Frank PF, Pierce WE. Antibiotic prophylaxis of carriers of sulfadiazine-resistant meningococci. *J Infect Dis* 1966; **116**: 473-480 [PMID: 5180145 DOI: 10.1093/infdis/116.4.473]

24 **Dworzack DL**, Sanders CC, Horowitz EA, Allais JM, Sookpranee M, Sanders WE, Ferraro FM. Evaluation of single-dose ciprofloxacin in the eradication of Neisseria meningitidis from nasopharyngeal carriers. *Antimicrob Agents Chemother* 1988; **32**: 1740-1741 [PMID: 3252755 DOI: 10.1128/AAC.32.11.1740]

25 **Girgis N**, Sultan Y, Frenck RW, El-Gendy A, Farid Z, Mateczun A. Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by Neisseria meningitidis. *Pediatr Infect Dis J* 1998; **17**: 816-819 [PMID: 9779768 DOI: 10.1097/00006454-199809000-00013]

26 **Guttler RB**, Counts GW, Avent CK, Beaty HN. Effect of rifampin and minocycline on meningococcal carrier rates. *J Infect Dis* 1971; **124**: 199-205 [PMID: 4942060 DOI: 10.1093/infdis/124.2.199]

27 **Judson FN**, Ehret JM. Single-dose ceftriaxone to eradicate pharyngeal Neisseria meningitidis. *Lancet* 1984; **2**: 1462-1463 [PMID: 6151066 DOI: 10.1016/S0140-6736(84)91647-7]

28 **Kaiser AB**, Hennekens CH, Saslaw MS, Hayes PS, Bennett JV. Seroepidemiology and chemoprophylaxis disease due to sulfonamide-resistant Neisseria meningitidis in a civillian population. *J Infect Dis* 1974; **130**: 217-224 [PMID: 4213375 DOI: 10.1093/infdis/130.3.217]

29 **Kaya A**, Tasyaran MA, Celebi S, Yilmaz S. Efficacy of a single dose of ciprofloxacin vs. rifampicin in eradicating the nasopharyngeal carriage of Neisseria meningitidis. *Turkish J Med Sci* 1997; **27**: 153-155

30 **Munford RS**, Sussuarana de Vasconcelos ZJ, Phillips CJ, Gelli DS, Gorman GW, Risi JB, Feldman RA. Eradication of carriage of Neisseria meningitidis in families: a study in Brazil. *J Infect Dis* 1974; **129**: 644-649 [PMID: 4209720 DOI: 10.1093/infdis/129.6.644]

31 **Pugsley MP**, Dworzack DL, Horowitz EA, Cuevas TA, Sanders WE, Sanders CC. Efficacy of ciprofloxacin in the treatment of nasopharyngeal carriers of Neisseria meningitidis. *J Infect Dis* 1987; **156**: 211-213 [PMID: 3110305 DOI: 10.1093/infdis/156.1.211]

32 **Pugsley MP**, Dworzack DL, Sanders CC, Sanders WE. Evaluation of Sch 29,482 in the eradication of Neisseria meningitidis from nasopharyngeal carriers. *Antimicrob Agents Chemother* 1984; **25**: 494-496 [PMID: 6732217 DOI: 10.1128/AAC.25.4.494]

33 **Renkonen OV**, Sivonen A, Visakorpi R. Effect of ciprofloxacin on carrier rate of Neisseria meningitidis in army recruits in Finland. *Antimicrob Agents Chemother* 1987; **31**: 962-963 [PMID: 3113331 DOI: 10.1128/AAC.31.6.962]

34 **Schwartz B**, Al-Tobaiqi A, Al-Ruwais A, Fontaine RE, A'ashi J, Hightower AW, Broome CV, Music SI. Comparative efficacy of ceftriaxone and rifampicin in eradicating pharyngeal carriage of group A Neisseria meningitidis. *Lancet* 1988; **1**: 1239-1242 [PMID: 2897515 DOI: 10.1016/S0140-6736(88)92069-7]

35 **Simmons G**, Jones N, Calder L. Equivalence of ceftriaxone and rifampicin in eliminating nasopharyngeal carriage of serogroup B Neisseria meningitidis. *J Antimicrob Chemother* 2000; **45**: 909-911 [PMID: 10837450 DOI: 10.1093/jac/45.6.909]

36 **Song F**, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009; **338**: b1147 [PMID: 19346285 DOI: 10.113/bmj.b1147]

37 **Dias S**, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; **33**: 607-617 [PMID: 23104435 DOI: 10.1177/0272989x12458724]

38 **Dias S**, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making* 2013; **33**: 618-640 [PMID: 23804507 DOI: 10.1177/0272989x13485157]

39 **Cooper NJ**, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med* 2009; **28**: 1861-1881 [PMID: 19399825 DOI: 10.1002/sim.3594]

40 **Xiong T**, Parekh-Bhurke S, Loke YK, Abdelhamid A, Sutton AJ, Eastwood AJ, Holland R, Chen YF, Walsh T, Glenny AM, Song F. Overall similarity and consistency assessment scores are not sufficiently accurate for predicting discrepancy between direct and indirect comparison estimates. *J Clin Epidemiol* 2013; **66**: 184-191 [PMID: 23186991 DOI: 10.1016/j.jclinepi.2012.06.022]

41 **Harbord RM**, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006; **25**: 3443-3457 [PMID: 16345038 DOI: 10.1002/sim.2380]

42 **Higgins JPT**, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from: URL: http//www.cochrane-handbook.org

43 **Zalmanovici Trestioreanu A**, Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. *Cochrane Database Syst Rev* 2011; **(8)**: CD004785 [PMID: 21833949 DOI: 10.1002/14651858.CD004785.pub4]

44 **Wu HM**, Harcourt BH, Hatcher CP, Wei SC, Novak RT, Wang X, Juni BA, Glennen A, Boxrud DJ, Rainbow J, Schmink S, Mair RD, Theodore MJ, Sander MA, Miller TK, Kruger K, Cohn AC, Clark TA, Messonnier NE, Mayer LW, Lynfield R. Emergence of ciprofloxacin-resistant Neisseria meningitidis in North America. *N Engl J Med* 2009; **360**: 886-892 [PMID: 19246360 DOI: 10.1056/NEJMoa0806414]

45 **Song F**, Xiong T, Parekh-Bhurke S, Loke YK, Sutton AJ, Eastwood AJ, Holland R, Chen YF, Glenny AM, Deeks JJ, Altman DG. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. *BMJ* 2011; **343**: d4909 [PMID: 21846695 DOI: 10.1136/bmj.d4909]

46 **Dias S**, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; **33**: 641-656 [PMID: 23804508 DOI: 10.1177/0272989x12455847]

47 **Donegan S**, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. *PLoS One* 2010; **5**: e11054 [PMID: 21085712 DOI: 10.1371/journal.pone.0011054]

48 **Jansen JP**, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C, Annemans L, Cappelleri JC. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011; **14**: 417-428 [PMID: 21669366 DOI: 10.1016/j.jval.2011.04.002]

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META-ANALYSIS

Daikenchuto for postoperative adhesive small bowel obstruction: A systematic review and meta-analysis

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Abstract

AIM

To assess the effectiveness of Daikenchuto for patients with postoperative adhesive small bowel obstruction (ASBO).

METHODS

A systematic search of PubMed (MEDLINE), CINAHL, the Cochrane Library and Ichushi Web was conducted, and the reference lists of review articles were hand-searched. The outcomes of interest were the incidence rate of surgery, the length of hospital days and mortality. The quality of the included studies, publication bias and between-study heterogeneity were also assessed.

RESULTS

Three randomized controlled trials (RCTs) and three retrospective cohort studies were selected for analysis. In the three RCTs, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.13; 95%CI: 0.03-0.50). Similarly, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.53; 95%CI: 0.32-0.87) in the three cohort studies. The length of hospital stay and mortality were not measured or described consistently.

CONCLUSION

The present meta-analysis demonstrates that administering Daikenchuto is associated with a lower incidence of surgery for patients with postoperative ASBO in the Japanese population. In order to better generalize these results, additional studies will be needed.

Key words: Herbal medicine; Kampo medicine; Postoperative adhesive small bowel obstruction; Systematic

review; Meta-analysis

Core tip: Daikenchuto, a traditional herbal medicine, is commonly used by gastroenterologists for postoperative adhesive small bowel obstruction in Japan. However, the effectiveness of Daikenchuto has not been systemically investigated. The systematic review and meta-analysis demonstrated that Daikenchuto is associated with a lower incidence of surgery for patients with postoperative adhesive bowel obstruction in the Japanese population.

Ukai T, Shikata S, Kassai R, Takemura Y. Daikenchuto for postoperative adhesive small bowel obstruction: A systematic review and meta-analysis. *World J Meta-Anal* 2016; 4(4): 88-94 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i4/88.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i4.88

INTRODUCTION

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery. ASBO accounts for up to 6% of all surgical admissions and 60% to 70% of small bowel obstruction[1,2]. Conservative management is chosen for patients with no strangulation or peritonitis, patients who underwent surgery more than six weeks before ASBO, patients with partial ASBO and patients with signs of resolution on admission[3]. Conservative management is successful in 73% to 90% of patients[4,5], but approximately one-fifth of patients later require surgery.

Essential conservative management includes decompression using a long tube or nasogastric tube intubation and intravenous fluid supplementation. According to guidelines for ASBO[3], other supplementary non-operative management options include water-soluble contrast agent administration[6], oral therapy with magnesium oxide, *Lactobacillus acidophilus* and simethicone[7], and hyperbaric oxygen therapy[8]. Water-soluble contrast agent administration, in particular, has the diagnostic value of predicting the need for surgery while the procedure itself also has therapeutic value[9].

Daikenchuto, a traditional herbal medicine, is frequently used by gastroenterologists in Japan for patients with ASBO[10] as well as chronic constipation, irritable bowel syndrome, Crohn's disease and paralytic ileus[11-14]. It comprises extract granules of processed ginger (kankyo), ginseng (ninjin) and zanthoxylum fruit (sansho). Basic research has shown several pharmacological mechanisms of Daikenchuto, including an increase in the blood flow of the intestinal tract, activation of intestinal motility, and prevention of bacterial translocation[15-17]. Recently, increasing evidence from clinical research has been accumulated[10]. However, while it is already widely used, no systematic analysis of the research has been conducted. The objective of this study was to examine the effectiveness of Daikenchuto in patients who developed postoperative ASBO.

MATERIALS AND METHODS

A systematic review was conducted, and the results were described according to the preferred reporting items for systematic reviews and meta-analyses statement[18].

Literature search

We systematically searched MEDLINE (PubMed), CINAHL, the Cochrane library and Ichushi Web, which is the largest medical article database in Japan, in November 2014. The MEDLINE search was conducted using the free-text words "Daikenchuto", "Dai-kenchu-to", "DKT" and "TJ-100". A similar literature search was conducted in the other three databases. References of review articles were also hand-searched.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the studies were randomized controlled trials (RCTs) or observational studies with exposure and control groups; (2) the participants were patients who developed postoperative ASBO; (3) daikenchuto was administered enterally; and (4) the study was performed in humans. No restriction was placed on the language. The exclusion criteria were as follows: (1) observational studies without controls; (2) Daikenchuto was administered to prevent postoperative adhesive small bowel obstruction; and (3) experimental animal research studies.

Outcome measures

The outcomes of interest were the incidence rate of surgery, the length of hospital stay, and mortality.

Quality assessment and data extraction

Two researchers (Ukai T and Shikata S) independently assessed the quality of each trial using the Critical Appraisal Skills Programme (CASP)[19] for RCTs and the Newcastle Ottawa Quality Assessment Scale (NOQAS)[20] for observational studies. The CASP asks six questions regarding the quality of RCTs. The NOQAS consists of three domains: Selection, comparability and outcome; the quality is assessed by the number of stars, with each domain having a maximum of four stars, two stars and three stars, respectively. The extracted data included the first author, year of publication, country, number of participants allocated to each group, and dosage of Daikenchuto.

Statistical analysis

The meta-analysis was conducted using the software Cochrane Collaboration Review Manager (version 5.3). All statistical analyses were performed using the Mantel-Haenszel method[21], and the summary statistics were described with odds ratios (ORs). An OR

Table 1 Characteristics of included studies

Ref.	Year	Country	Study design	Dose (g)	No. of patients with Daikenchuto (surgery: No surgery)	No. of patients without Daikenchuto (surgery: No surgery)	OR (95%CI)
Oyabu *et al*[23]	1995	Japan	RCT	15	1:27	5:20	0.15 (0.02-1.37)
Kubo *et al*[24]	1995	Japan	RCT	15	1:17	2:10	0.29 (0.02-3.67)
Itoh*et al*[25]	2002	Japan	RCT	15	5:8	10:1	0.06 (0.01-0.65)
Moriwaki *et al*[26]	1992	Japan	Retrospective cohort	15	1:23	49:154	0.14 (0.02-1.04)
Furukawa *et al*[27]	1995	Japan	Retrospective cohort	7.5-15.0	6:20	26:49	0.57 (0.20-1.58)
Yasunaga *et al*[28]	2011	Japan	Retrospective cohort	Not mentioned	20:124	28:116	0.67 (0.36-1.25)

RCT: Randomized controlled trial.

Table 2 Critical appraisal for randomized controlled trials using critical appraisal skills program

	Oyabu *et al*[23]	Kubo *et al*[24]	Itoh *et al*[25]
1 Was the assignment of patients to treatments randomized?	Y	Y	Y
2 And if so, was the randomization list concealed (blinded or masked) to those deciding on patient eligibility for the study?	Y	Y	-
3 Were all patients analysed in the groups to which they were randomized (was an "intention to treat" analysis used)?	Y	N	Y
4 Were patients in the treatment and control groups similar with respect to known prognostic factors?	Y	Y	Y
5 Were patients, clinicians and outcome assessors kept "blind" to which treatment was being received?	-	-	-
6 Was follow-up complete?	Y	Y	Y

Y: Yes; N: No.

less than one favored the intervention group, and the point estimate of the OR was considered statistically significant at the 0.05 level if the 95%CI did not include the value of one. A fixed-effects model was initially adapted for all outcome measures. We tested for homogeneity among the studies by calculating the I^2 value. I^2 can be calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom[22]. We defined I^2 values of less than 25% as low heterogeneity, 25% to 50% as moderate heterogeneity and more than 50% as high heterogeneity[22]. If the hypothesis of homogeneity was rejected, a random-effects model was employed.

RESULTS

The search strategy yielded 1507 articles (Figure 1). After duplications were removed, we checked the title and abstract of the articles according to the inclusion and exclusion criteria. Full texts of the remaining articles were read, and three RCTs[23-25] and three cohort studies[26-28] were chosen based on the inclusion and exclusion criteria. Finally, the data were extracted from the studies (Table 1).

The publication year ranged from 1992 to 2011, and all research was conducted in Japan. All studies compared patients who were administered Daikenchuto with patients who were not administered Daikenchuto. The dosage of Daikenchuto was 15.0 g in four studies[23-26], 7.5-15.0 g in one study[27], and unreported in one study[28]. Daikenchuto was administered orally in one study[25], through a tube in three studies[23,24,28], or both in one study[26]. Participants were chosen regardless of the kind of abdominal surgical history in five studies[23-27], whereas only patients with a history of colorectal cancer were chosen in one study[28]. None of the included studies described the criteria of diagnosis of ASBO or pre-defined decision process for proceeding to surgery. The funnel plot of publication bias is shown in Figure 2.

Quality assessment for selected articles

Among the three RCTs, one was conducted at multiple hospitals[24], and the other two were conducted at one hospital[23,25]. In two RCTs[23,24], patients were randomly assigned using a concealed envelope, and in a third study[25], the method of assignment was not described. None of these articles mentioned the method of blinding. Patient follow-up continued until the obstruction was released and symptoms were relieved or until the patient underwent a surgery to remove the obstruction. In one trial[23], the reasons for the surgical intervention were retrospectively explained, but no explanation was provided in the other two studies[24,25]. An intention-to-treat analysis was not used in one study[24] (Table 2).

Of the three retrospective cohort studies, one was conducted using a national inpatient database using propensity score analysis[28], and both the exposure and control groups were recruited at one or several hospitals in a community[26,27]. Regarding outcome domains, the criteria for the decisions to proceed to surgery for the ASBO were not described in any of the three studies (Table 3).

Incidence of surgery in the RCTs

A total of 107 patients were included in the three

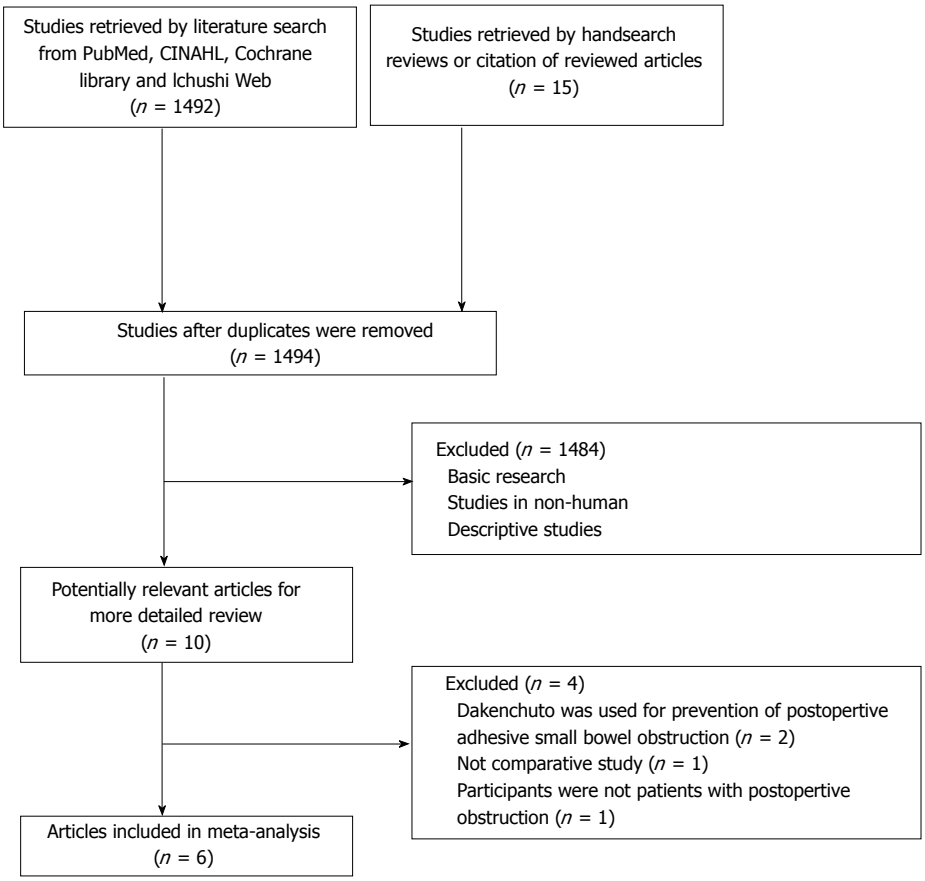

Figure 1 Search strategy according to the preferred reporting items for systematic review and meta-analyses.

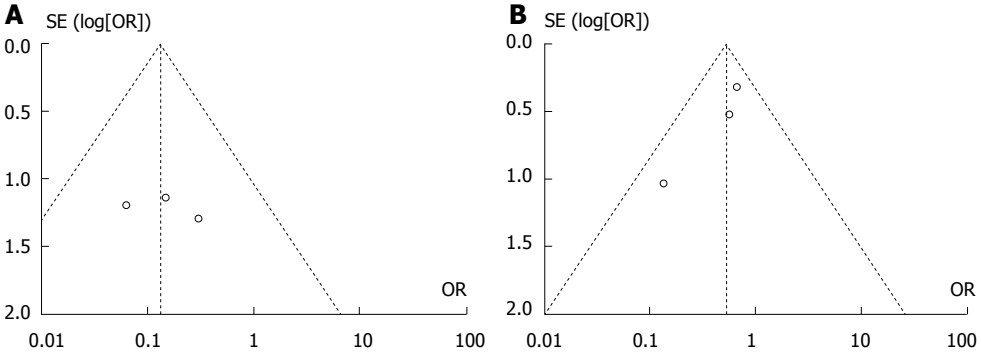

Figure 2 Funnel plot of randomized controlled trials (A) and cohort studies (B) reporting the risk of surgery in patients with postoperative adhesive small bowel obstruction given Daikenchuto. OR: Odds ratio; SE: Standard error.

RCTs (Figure 3). In the Daikenchuto group, seven of 59 (11.9%) patients eventually underwent surgery for the ASBO, whereas 17 of 48 (35.4%) patients underwent surgery in the control group. The overall OR was 0.13 (95%CI: 0.03-0.50), demonstrating statistical significance. There was no heterogeneity among the trials (I^2 = 0%).

Incidence of surgery in the cohort studies

A total of 616 patients were included in the three cohort studies (Figure 4). The incidences of surgical intervention were 27 of 194 (13.9%) in the Daikenchuto group and 103 of 422 (24.4%) in the control group. The overall OR was 0.53 (95%CI: 0.32-0.87), also demonstrating statistical significance. There was low heterogeneity among the trials (I^2 = 12%).

Other outcomes

Mortality was described in the one cohort study with a total of 288 patients[28]. The number of deaths identified was four (2.8%) in the Daikenchuto group and two (1.4%) in the control group, and this difference was not found to be significant.

Length of hospital stay was described in two studies. One RCT[27] showed that the length of the hospital stay was 5.90 d shorter (95%CI: 4.77-7.03) in the

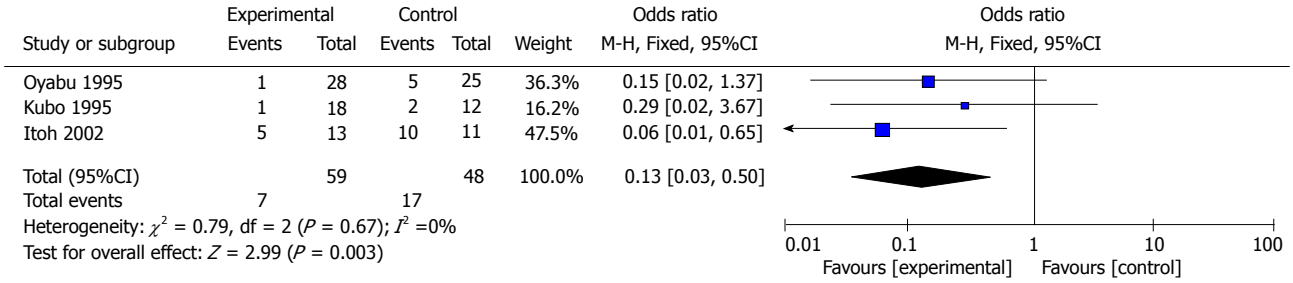

Figure 3 Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from randomized controlled trials. Boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CI. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.

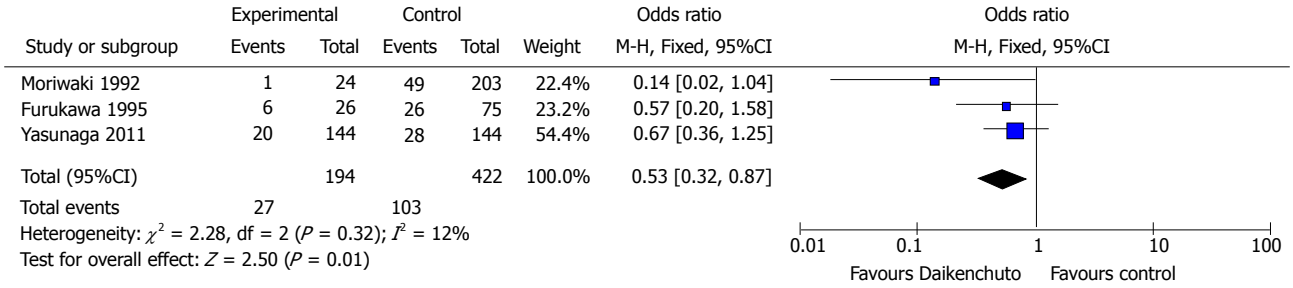

Figure 4 Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from cohort studies boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CIs. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.

Table 3 Critical appraisal for cohort studies using newcastle ottawa quality assessment scale

	Moriwaki *et al*[26]	Furukawa *et al*[27]	Yasunaga *et al*[28]
Selection			
Representativeness of the exposed cohort			Y
Selection of non-exposed cohort	Y	Y	Y
Ascertainment of exposure	Y	Y	Y
Demonstration that outcome of interest was not present at start of study	Y	Y	Y
Comparability			
Comparability of cohorts on the basis of the design or analysis	Y	Y	Y
Outcome			
Assessment of outcome			
Was follow-up long enough to occur	Y	Y	Y
Adequacy of follow up of cohorts	Y	Y	Y

Y: Yes.

Daikenchuto group. Also, one cohort study[28] showed statistical significance in favor of the Daikenchuto group using Kaplan-Meier methods and log-rank test (P = 0.018).

DISCUSSION

This systematic review provides evidence from three RCTs and three cohort studies conducted in Japan concerning the effectiveness of the traditional herbal medicine Daikenchuto in reducing the risk of surgery for patients with postoperative ASBO. From the synthesized results, ASBO patients who received Daikenchuto had a significantly lower risk of surgery. The study assessed RCTs and cohort studies individually, and they provided consistent results.

Potential benefit of daikenchuto

There are several treatment options recommended in guidelines for ASBO[3]. Among the options, water-soluble contrast agent administration is highly recommended because there is robust evidence for its efficacy both in predicting a need for surgery and for preventing surgery[9]. However, despite its established efficacy, 20.8% of ASBO patients treated this way proceed to surgery[9]. Daikenchuto has widely been used in Japan and has a low risk of side effects[29], and the cost is only 145.5 JPY (US$1.25) per day. From these perspectives, Daikenchuto could be used as part of initial non-operative management adjunct to water-soluble contrast

administration. It is potentially useful for patients who have a high risk of anaphylactoid reaction to water-soluble contrast agent or patients who cannot tolerate surgery.

Traditional herbal medicine in Japan

Traditional Japanese herbal medicine is known as Kampo medicine. Kampo medicine has its roots in traditional Chinese medicine and was introduced to Japan in the middle of the sixth century. The Japanese Ministry of Health, Labour and Welfare has officially approved 212 types of Kampo medicines, and these medicines are covered by the National Health Insurance programme[30]. All certified medical doctors can prescribe both Western and Kampo medicines, and they choose the optimal one depending on the condition of the patients. Kampo medicine is referred to as an alternative medicine, but in practice, Japanese physicians use both Western medicine and Kampo medicine; in particular, Kampo medicine is commonly used for patients with medically unexplained symptoms that Western medicine often fails to solve[10]. The mechanism of the pharmacological effect is becoming clear, but more clinical research is needed before Kampo medicine will be widely adopted in other countries.

Limitations

This study has several limitations. First, the included studies have methodological problems. None of included three RCTs described the blinding of clinicians and assessors. Also, none of the included studies described the criteria of decisions of proceeding to surgery. Since the decision to proceed to surgery can be subjective, there may be bias in this outcome statistic, especially when clinicians were not blinded.

Second, the reviewed studies were conducted in Japan using Japanese populations. In three studies[23,25,26], participants were recruited at one hospital. These facts pose the question of generalizability. Thus, additional evidence is needed from patients in other countries.

Finally, all studies included compared those patients who were administered Daikenchuto and who were not. We could not find studies that compared Daikenchuto and water-soluble contrast agent. Since administering water-soluble contrast agent is the standard of care, Daikenchuto and water-soluble contrast agent should be directly compared before it is applied to clinical practice.

The traditional herbal medicine Daikenchuto significantly reduces the risk of surgery for patients with postoperative ASBO in a Japanese population. In order to better generalize these results, additional studies incorporating a broader set of outcomes and an expanded population base will be needed.

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COMMENTS

Background

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery, and one fifth of them later require surgery. Daikenchuto, a traditional herbal medicine, is commonly used for postoperative adhesive small bowel obstruction, but the effectiveness of Dakenchuto in preventing surgery for patients with postoperative ASBO is not systemically assessed.

Research frontiers

Evidence in traditional herbal medicine from clinical research, as well as basic research has increasingly been accumulated. However, the evidence is not systemically collected and integrated.

Innovations and breakthroughs

In the present study, the authors demonstrated the effectiveness of Daikenchuto for preventing patients by pooling results from randomized controlled trials and cohort studies. This is the first report of meta-analysis to assess the traditional herbal medicine, Daikenchuto.

Applications

The present study allows understanding the role of Daikenchuto for patients with postoperative ASBO to prevent surgery.

Peer-review

It is a very interesting paper and a new approach to manage the adhesive small bowel obstruction.

REFERENCES

1 **Parker MC**, Ellis H, Moran BJ, Thompson JN, Wilson MS, Menzies D, McGuire A, Lower AM, Hawthorn RJ, O'Briena F, Buchan S, Crowe AM. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. *Dis Colon Rectum* 2001; **44**: 822-829; discussion 829-830 [PMID: 11391142]

2 **Stanciu D**, Menzies D. The magnitude of adhesion-related problems. *Colorectal Dis* 2007; **9** Suppl 2: 35-38 [PMID: 17824968 DOI: 10.1111/j.1463-1318.2007.01346.x]

3 **Di Saverio S**, Coccolini F, Galati M, Smerieri N, Biffl WL, Ansaloni L, Tugnoli G, Velmahos GC, Sartelli M, Bendinelli C, Fraga GP, Kelly MD, Moore FA, Mandalà V, Mandalà S, Masetti M, Jovine E, Pinna AD, Peitzman AB, Leppaniemi A, Sugarbaker PH, Goor HV, Moore EE, Jeekel J, Catena F. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2013 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. *World J Emerg Surg* 2013; **8**: 42 [PMID: 24112637 DOI: 10.1186/1749-7922-8-42]

4 **Seror D**, Feigin E, Szold A, Allweis TM, Carmon M, Nissan S, Freund HR. How conservatively can postoperative small bowel obstruction be treated? *Am J Surg* 1993; **165**: 121-125; discussion 125-126 [PMID: 8418687]

5 **Brolin RE**. Partial small bowel obstruction. *Surgery* 1984; **95**: 145-149 [PMID: 6695331]

6 **Abbas SM**, Bissett IP, Parry BR. Meta-analysis of oral water-soluble contrast agent in the management of adhesive small bowel obstruction. *Br J Surg* 2007; **94**: 404-411 [PMID: 17380561 DOI: 10.1002/bjs.5775]

7 **Chen SC**, Yen ZS, Lee CC, Liu YP, Chen WJ, Lai HS, Lin FY, Chen WJ. Nonsurgical management of partial adhesive small-bowel obstruction with oral therapy: a randomized controlled trial. *CMAJ* 2005; **173**: 1165-1169 [PMID: 16275967 DOI: 10.1503/cmaj.1041315]

8 **Ambiru S**, Furuyama N, Kimura F, Shimizu H, Yoshidome H, Miyazaki M, Ochiai T. Effect of hyperbaric oxygen therapy on patients with adhesive intestinal obstruction associated with abdominal surgery who have failed to respond to more than 7 days of conservative treatment. *Hepatogastroenterology* 2008; **55**:

491-495 [PMID: 18613394]
9 **Branco BC**, Barmparas G, Schnüriger B, Inaba K, Chan LS, Demetriades D. Systematic review and meta-analysis of the diagnostic and therapeutic role of water-soluble contrast agent in adhesive small bowel obstruction. *Br J Surg* 2010; **97**: 470-478 [PMID: 20205228 DOI: 10.1002/bjs.7019]
10 **Tominaga K**, Arakawa T. Kampo medicines for gastrointestinal tract disorders: a review of basic science and clinical evidence and their future application. *J Gastroenterol* 2013; **48**: 452-462 [PMID: 23503839 DOI: 10.1007/s00535-013-0788-z]
11 **Nakamura T**, Sakai A, Isogami I, Noda K, Ueno K, Yano S. Abatement of morphine-induced slowing in gastrointestinal transit by Dai-kenchu-to, a traditional Japanese herbal medicine. *Jpn J Pharmacol* 2002; **88**: 217-221 [PMID: 11928724]
12 **Ohya T**, Usui Y, Arii S, Iwai T, Susumu T. Effect of dai-kenchu-to on obstructive bowel disease in children. *Am J Chin Med* 2003; **31**: 129-135 [PMID: 12723762 DOI: 10.1142/s0192415x03000710]
13 **Iwai N**, Kume Y, Kimura O, Ono S, Aoi S, Tsuda T. Effects of herbal medicine Dai-Kenchu-to on anorectal function in children with severe constipation. *Eur J Pediatr Surg* 2007; **17**: 115-118 [PMID: 17503305 DOI: 10.1055/s-2007-965016]
14 **Shimada M**, Morine Y, Nagano H, Hatano E, Kaiho T, Miyazaki M, Kono T, Kamiyama T, Morita S, Sakamoto J, Kusano M, Saji S, Kanematsu T, Kitajima M. Effect of TU-100, a traditional Japanese medicine, administered after hepatic resection in patients with liver cancer: a multi-center, phase III trial (JFMC40-1001). *Int J Clin Oncol* 2015; **20**: 95-104 [PMID: 24595550 DOI: 10.1007/s10147-014-0678-2]
15 **Kono T**, Kanematsu T, Kitajima M. Exodus of Kampo, traditional Japanese medicine, from the complementary and alternative medicines: is it time yet? *Surgery* 2009; **146**: 837-840 [PMID: 19744449 DOI: 10.1016/j.surg.2009.06.012]
16 **Shibata C**, Sasaki I, Naito H, Ueno T, Matsuno S. The herbal medicine Dai-Kenchu-Tou stimulates upper gut motility through cholinergic and 5-hydroxytryptamine 3 receptors in conscious dogs. *Surgery* 1999; **126**: 918-924 [PMID: 10568192]
17 **Yoshikawa K**, Kurita N, Higashijima J, Miyatani T, Miyamoto H, Nishioka M, Shimada M. Kampo medicine "Dai-kenchu-to" prevents bacterial translocation in rats. *Dig Dis Sci* 2008; **53**: 1824-1831 [PMID: 18446437 DOI: 10.1007/s10620-008-0281-3]
18 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**: W65-W94 [PMID: 19622512]
19 **Critical Appraisal Skills Programme (CASP)**. Available from: URL: http://www.csh.org.tw/into/medline/WORD.pdf
20 **Ottawa Hospital Research Institute**. Available from: URL: http://www.ohri.ca/home.asp
21 **ManteL N**, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719-748 [PMID: 13655060]
22 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]
23 **Oyabu H**, Matsuda S, Kurisu S, Hatta K, Koyama T, Kita Y, Umeki M, Kihana E, Miyamoto K, Otaki Y, Ishida T, Kurose H. A randomized control trial for effectiveness of Daikenchuto in patinets with postoperative adhesive small bowel obstruction. *Prog Med* 1995; **15**: 1954-1958
24 **Kubo N**, Uchida Y, Akiyoshi T, Miyahara M, Shibata Y, Nakano S. Effect of Daikenchuto on bowel obstruction. *Prog Med* 1995; **15**: 1962-1967
25 **Itoh T**, Yamakawa J, Mai M, Yamaguchi N, Kanda T. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. *J Int Med Res* 2002; **30**: 428-432 [PMID: 12235926]
26 **Moriwaki Y**, Yamamoto T, Katamura H, Sugiyama M. Clinical Resarch of the Effect of Dai-Kenchuto for Simple Intestinal Obstruction. *Kampo Med* 1992; **43**: 303-308 [DOI: 10.3937/kampomed.43.303]
27 **Furukawa Y**, Siga Y, Hanyu N, Hahimoto N, Mukai H, Nishikawa K, Aoki H. The effect of Daikenchuto on intestinal motility and on the treatment of postoperative bowel obstruction. *Japanese J Gastroent Surg* 1995; **28**: 956-960
28 **Yasunaga H**, Miyata H, Horiguchi H, Kuwabara K, Hashimoto H, Matsuda S. Effect of the Japanese herbal kampo medicine dai-kenchu-to on postoperative adhesive small bowel obstruction requiring long-tube decompression: a propensity score analysis. *Evid Based Complement Alternat Med* 2011; **2011**: 264289 [PMID: 21584269 DOI: 10.1155/2011/264289]
29 **Suzuki H**, Inadomi JM, Hibi T. Japanese herbal medicine in functional gastrointestinal disorders. *Neurogastroenterol Motil* 2009; **21**: 688-696 [PMID: 19563404 DOI: 10.1111/j.1365-2982.2009.01290.x]
30 **Okamoto H**, Iyo M, Ueda K, Han C, Hirasaki Y, Namiki T. Yokukan-san: a review of the evidence for use of this Kampo herbal formula in dementia and psychiatric conditions. *Neuropsychiatr Dis Treat* 2014; **10**: 1727-1742 [PMID: 25246794 DOI: 10.2147/NDT.S65257]

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META-ANALYSIS

Gadoxetic acid-enhanced magnetic resonance imaging for the detection of small hepatocellular carcinoma (≤ 2.0 cm) in patients with chronic liver disease: A meta-analysis

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Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this study.

Data sharing statement: Supplementary files provide detailed description of 10 studies included in the meta-analysis.

Manuscript source: Unsolicited manuscript

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Abstract

AIM

To perform a meta-analysis assessing the value of gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) in detecting small hepatocellular carcinoma (HCC) (≤ 2.0 cm) in patients with chronic liver disease.

METHODS

Databases, including MEDLINE and EMBASE, were searched for relevant original articles published from January 2008 to February 2015. Data were extracted, and summary estimates of diagnostic accuracy indexes such as sensitivity, specificity, diagnostic odds ratio, predictive value, and areas under summary receiver operating characteristic curve were obtained using a random-effects model, with further exploration employing meta-regression and subgroup analyses.

RESULTS

In 10 studies evaluating 768 patients, pooled per-lesion sensitivity of Gd-EOB-DTPA was 91% (95%CI: 83%-95%), with a specificity of 95% (95%CI: 87%-98%). Overall positive likelihood ratio was 18.1 (95%CI: 6.6-49.4), for negative likelihood ratio (NLR) of 0.10 (95%CI: 0.05-0.19) and diagnostic odds ratio of 182 (95%CI: 57-581). Subgroup analysis suggested that diagnostic performance of Gd-EOB-MRI for sub-centimeter HCC (≤ 1.0 cm) detection was low, with a sensitivity of 69% (95%CI: 59%-78%). In studies with both Gd-EOB-MRI and diffusion-weighted imaging (DWI) performed, Gd-EOB-MRI/DWI combination was more sensitive than Gd-EOB-DTPA alone, whether for small lesions (86% *vs* 77%) or sub-centimeter ones (80% *vs* 56%).

CONCLUSION
A limited number of small studies suggested that Gd-EOB-MRI has good diagnostic performance in the detection of small HCC (≤ 2.0 cm) among patients with chronic liver disease, but relatively lower performance for detection of sub-centimeter HCC (≤ 1.0 cm). Combination of Gd-EOB-MRI and DWI can improve the diagnostic sensitivity of MRI.

Key words: Liver-specific agent; Gadoxetic acid-enhanced Magnetic resonance imaging; Hepatocellular carcinoma; Meta-analysis

Core tip: Although studies have shown that gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) had good diagnostic performance in detecting hepatocellular carcinoma (HCC), the results about small HCC have been limited thus far by a small number of included patients, especially for subcentimeter lesion (≤ 1.0 cm). Therefore, we performed a systematic review and meta-analysis to obtain updated diagnostic performance values of Gd-EOB-MRI for the detection of small HCC in terms of different size (≤ 2.0 cm *vs* ≤ 1.0 cm), different technique (Gd-EOB-MRI alone *vs* combined diffusion weighted imaging).

Shan Y, Gao J, Zeng MS, Lin J, Xu PJ. Gadoxetic acid-enhanced magnetic resonance imaging for the detection of small hepatocellular carcinoma (≤ 2.0 cm) in patients with chronic liver disease: A meta-analysis. *World J Meta-Anal* 2016; 4(4): 95-104 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i4/95.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i4.95

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related deaths worldwide[1]. Despite important advances in multidisciplinary therapies, complete curative treatment of early-stage small HCC (≤ 2.0 cm, including hypervascular and hypovascular HCC) remains the only option for long-term patient survival. Studies indicated that the smaller the HCC, the less likely the occurrence of microvascular invasion[2]. The International Consensus Group for Hepatocellular Neoplasia also stated that early HCC, well differentiated HCC with a vaguely nodular appearance and less than 2 cm in size, should be considered a carcinoma *in situ*, and is characterized by an indistinct margin without capsule formation, vascular invasion or intrahepatic metastasis[3,4]. In addition, the smaller the HCC, the more likely it is for local ablation to be complete[5,6]. It is therefore important to perform early diagnosis of HCC when the tumor is still as small as possible. However, in small nodules (≤ 2.0 cm), an atypical vascular profile is not uncommon, which constitutes a challenge for definitive radiological diagnosis. These lesions may, in fact, represent either early HCCs or preneoplastic lesions, such as high-grade dysplastic nodules[3,7,8]. They are often hypovascular and lack arterial enhancement or a washout pattern[7,8]. In addition, many small, benign nodules (*e.g.,* cirrhosis-related nodules and arterioportal shunts) can mimic small HCC in patients with cirrhosis.

The hepatocyte-specific magnetic resonance imaging (MRI) contrast agent gadoxetic acid (Gd-EOB-DTPA; Bayer Healthcare, Berlin, Germany) can provide, in a single examination, comprehensive hemodynamic information during early dynamic phases and improved lesion detection in the hepatobiliary phase (HBP)[9-11]. HBP images better depict HCC, which appears as a hypointense lesion, compared with conventional dynamic gadolinium-enhanced images, on which small HCCs frequently show only arterial enhancement without early washout[12-14].

Although studies have compared gadoxetic acid-enhanced MRI (Gd-EOB-MRI) with multidetector computed tomography (MDCT) and Gd-DTPA-enhanced MRI for detecting small HCC, and shown that HBP imaging provides a slight improvement in the diagnosis of small HCC[10,11,15-22], the results were limited thus far by the small numbers of included patients, especially for sub-centimeter lesions (≤ 1.0 cm). Therefore, we performed a systematic review and meta-analysis of the literature published in the past few years, to obtain updated diagnostic performance values of Gd-EOB-MRI for detecting small HCC in patients with chronic liver disease.

MATERIALS AND METHODS

Literature search

A comprehensive literature search of studies evaluating human subjects was performed by two investigators (Yan Shan and Peng-Ju Xu) to identify articles on diagnostic performance of Gd-EOB-MRI in detecting small HCC in patients with chronic liver disease. The PubMed and EMBASE databases were searched from January 2008 to February 2015, for English articles with the following keywords: (Gd-EOB-DTPA or gadoxetic acid or gadoxetate disodium or Gd-EOB-MRI) and (hepatocellular carcinoma or liver neoplasms) and (sensitivity or specificity or false negative or false positive or diagnosis or detection or accuracy). Other databases, such as Web of Science, Scopus and the Cochrane Database of systematic review, were also searched for relevant articles. All review articles, comments, case reports, letters, and unpublished articles were eliminated. Articles found to be eligible based on title, and subsequently abstract, were then selected to determine further suitability for inclusion in this study.

Inclusion and exclusion criteria

Studies were included if, in addition, all the following inclusion criteria were met: (1) articles reported in

English; (2) Gd-EOB-MRI with HBP performed to evaluate small HCC in patients with chronic liver disease; (3) histopathology analysis and/or cross-sectional imaging follow-up used as the reference standard; (4) data based on per-lesion basis; and (5) sufficient data reported to construct 2 × 2 contingency tables. Authors of studies with insufficient published data were contacted personally in an effort to retrieve the missing data. Studies were excluded if either of the following exclusion criteria were applicable: (1) fewer than 10 patients; or (2) multiple reports published for the same study population (in this case, the publication with the most details and/or most recently published was selected).

Data extraction and quality assessment

The methodological quality of the included studies was assessed independently by the same two investigators using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool in Review Manager 5.3, which evaluates the risk of bias for four domains and clinical applicability for three domains of study characteristics. The QUADAS-2 tool was used as provided by the QUADAS-2 group[23]. Meanwhile, relevant data were also extracted from each study, including author, publication year, sample size, number of lesion, description of study population (age and gender), study design (case series, case control, cohort study, and randomized controlled trial), patient enrollment (consecutive or not), etiology of liver disease, magnetic field strength, dose of Gd-EOB-DTPA, number of experts who assessed and interpreted Gd-EOB-MRI data, and mean time interval between Gd-EOB-MRI and histopathology. Any mention Gd-EOB-MRI measurement blinding to histopathologic and clinical results and/or other diagnostic methods used was also recorded. For each study, the number of true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) findings was recorded for Gd-EOB-MRI in detecting small HCC in patients with chronic liver disease. Disagreements were resolved by discussion between the two investigators.

Statistical analysis

Diagnostic accuracy: Data regarding diagnostic performance of Gd-EOB-MRI were combined quantitatively across eligible studies. In addition, bivariate random-effects model and hierarchical summary receiver operating characteristic (ROC) were used to obtain summary estimates of sensitivity and specificity[24]. Diagnostic odds ratio (DOR) and likelihood ratios are also metrics that combine both sensitivity and specificity in calculations.

Heterogeneity exploration and subgroup analysis: Heterogeneity was assessed by likelihood χ^2 tests and I^2. The I^2 index is a measure of the percentage of total variation across studies due to heterogeneity beyond chance. Values of 30%-60%, 50%-90%, and 75%-100% may represent moderate, substantial and considerable heterogeneity, respectively[25]. In likelihood ratio χ^2 tests, $P < 0.05$ was regarded as indicative of apparent heterogeneity. The threshold effect is an important extra source of variation in meta-analysis. If there is a threshold effect, an inverse correlation appears; in this case, combining study results involving fitting a ROC curve was better than pooling sensitivities and specificities. To assess threshold effect existence, sensitivity and specificity for Gd-EOB-MRI were plotted on an ROC plane[26]. Moreover, Spearman correlation coefficient (between the logit of sensitivity and that of specificity) was determined for Gd-EOB-MRI. In case no threshold effect was found in the meta-analysis, meta-regression analysis with a backward stepwise algorithm was then performed to investigate other sources of heterogeneity for Gd-EOB-MRI. Such factors included the type of study design (case series, case control, cohort study, and randomized controlled trial), use of the same reference standard, enrollment patients, age (year), gender, sample size, number of lesions, diameter of HCC, MRI field strength, dose of Gd-EOB-DTPA, mean time interval between Gd-EOB-MRI and histopathology, reviewers (year of experience), and publication year.

Subgroup analysis was performed according to lesion size ($\leqslant$ 2.0 cm *vs* $\leqslant$ 1.0 cm); We also compared the performance of Gd-EOB-MRI alone with that of its combination with DWI by analyzing studies that used these diagnostic methods in the same patients.

Publication bias: Publication bias was assessed visually using a scatterplot of the inverse of the square root of the effective sample size ($1/ESS^{1/2}$) against diagnostic log odds ratio, which should have a symmetric funnel shape when no publication bias is present. Formal testing for publication bias was conducted using a regression of diagnostic log odds ratio against $1/ESS^{1/2}$ and weighting according to the effective sample size, with $P < 0.01$ indicating significant asymmetry[27].

Statistical analysis was performed with Stata statistical software Version 12 (StataCorp LP, Texas, United States) and Meta-DiSc statistical software, version 1.4 (Unit of Clinical Biostatistics, Ramo'n y Cajal Hospital, Madrid, Spain). $P < 0.05$ was considered statistically significant.

RESULTS

Literature search and study selection

After a comprehensive computerized search was performed, with reference lists extensively cross-checked, this research yielded 387 primary studies; 265 studies were excluded after title and abstract review. One handred twelve articles were excluded after reviewing the full article for the following reasons: (1) study aim did not reveal Gd-EOB-MRI in detecting HCC (n = 45); (2) results were obtained from a combination of HCC, hepatic metastasis and other hepatic diseases that could not be differentiated for assessment of single disease (n = 9); (3) no results regarding Gd-EOB-DTPA

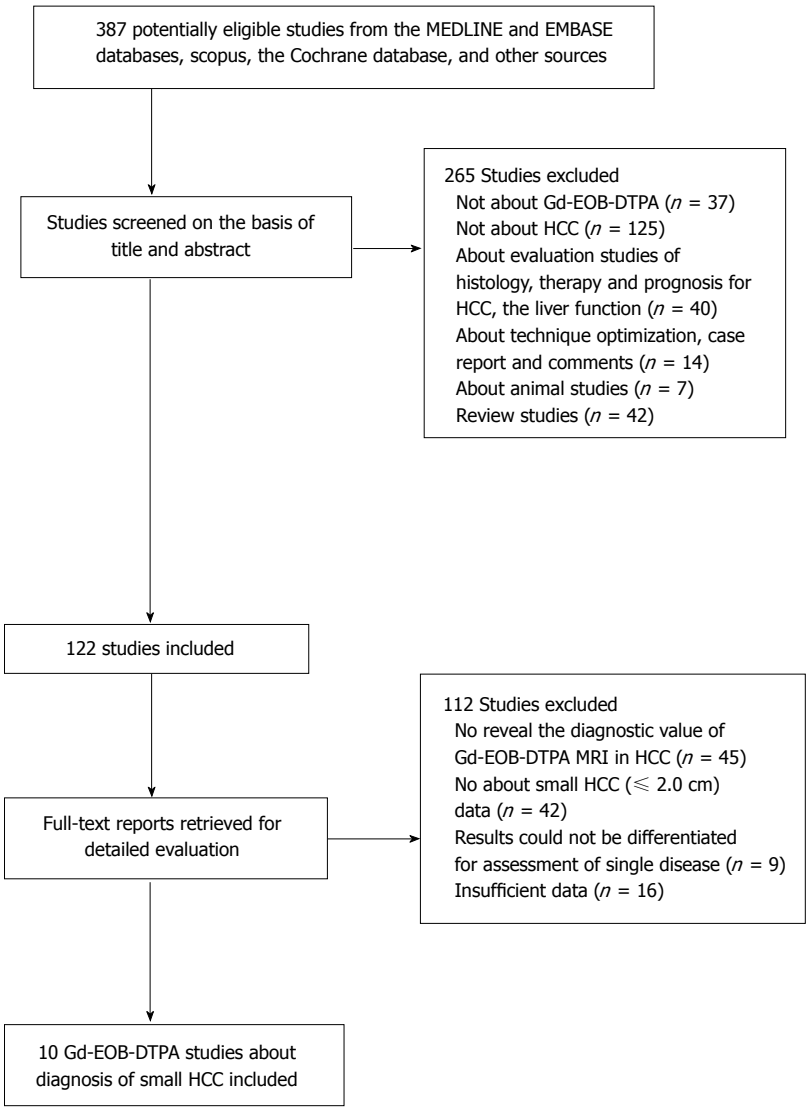

Figure 1 Flow chart for articles identified and included in this meta-analysis. HCC: Hepatocellular carcinoma.

in diagnosis of small HCC (n = 42); and (4) too little data reported to allow construction of a 2 × 2 table of TP, FN, FP and TN values (n = 16). Therefore, a total of 10 studies[9-11,17-21,28,29], which fulfilled all inclusion criteria, were considered for the analysis. The detailed procedure of study selection in the meta-analysis is shown in Figure 1.

Study description

The important characteristics of the included studies are detailed in Supplement file for review. In brief, there were no cohort or randomized controlled studies. Most studies were case series. Of all 10 studies, 7 enrolled patients retrospectively[9,11,18-21,29], while 3 stated that they were prospective[10,17,28]. All 10 studies enrolled patients in a consecutive manner[9-11,17-21,28,29]. A total of 768 patients were enrolled in the eligible studies.

There were 5 studies with MRI examinations performed with a 1.5 Tesla device[9,10,17,19,20]; 4 studies performed MRI examinations with 3.0 Tesla devices[11,18,21,29]. In the remaining study, MRI examinations were performed with 3.0 Tesla device in comparison with 1.5 Tesla device[28]. One report used a fixed dose of 10 mL of Gd-EOB-DTPA[11], while in the other 9, Gd-EOB-DTPA was administrated according to the manufacturer's instructions at 0.025 mmol per kilogram body weight. Evaluation of Gd-EOB-DTPA results was carried out in a blinded fashion in all 10 studies[9-11,17-21,28,29]. The reference standard depended solely on explanted livers in only two studies[20,21].

Assessment of study quality and publication bias

Study quality assessment data obtained with the QUADAS-2 tool are summarized in Figure 2. There were no studies considered to be at low risk of bias for all domains. The included studies being case series or of case-control design, a high risk of bias for patient selection was introduced. The substantial risk of bias regarding patient flow and timing mainly arose from that more than half of these studies used a combination of histopathologic findings and cross-section imaging follow-up as reference standards; this may result in verification bias. There was also a considerable risk of bias regarding the reference standard, as 2 studies reported that the pathologist was not blinded to imaging test results, while 4 others did not mention pathologist

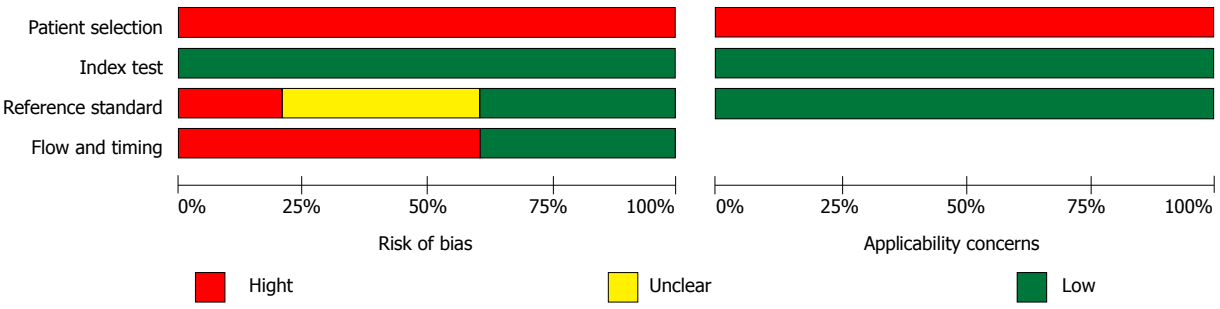

Figure 2 Grouped bar charts showing results of study quality assessment with the QUADAS-2 tool. The charts show the cumulative results of the 10 included studies in terms of risk of bias (left) and concerns regarding applicability (right) according to each QUADAS-2 domain.

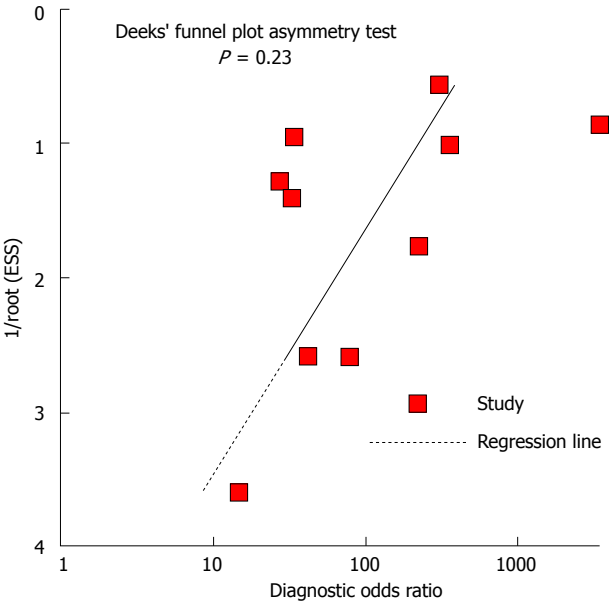

Figure 3 Results of Deeks' funnel plot asymmetry test for publication bias. The nonsignificant slope indicates that no significant bias was found. ESS: Effective sample size (P = 0.23).

blinding to index test results.

A nonsignificant slope was obtained for Deeks' funnel plot asymmetry tests (Figure 3), indicating that no significant bias was found (P = 0.23).

Diagnostic performance of Gd-EOB-MRI in detecting small HCC

Overall small HCC (≤ 2.0 cm): When studies used multiple readers, giving a range of accuracy, we selected the average result for analysis. Pooled sensitivity of Gd-EOB-MRI was 0.91 (95%CI: 0.83-0.95), for a specificity of 0.95 (95%CI: 0.87-0.98). DOR was 182 (95%CI: 57-581). The detailed sensitivity and specificity data, with 95%CIs for each individual study are provided as a Forest plot in Figure 4. Likelihood ratio syntheses yielded an overall positive likelihood ratio (PLR) of 18.1 (95%CI: 6.6-49.4) and negative likelihood ratio (NLR) of 0.10 (95%CI: 0.05-0.19). The scattergram of PLR and NLR is shown in Figure 5.

Hierarchical summary receiver operator characteristic (HSROC) curves (Figure 6) showed good diagnostic performance for Gd-EOB-MRI for all the studies combined. The area under the curve of the HSROC was 0.97 (95%CI: 0.96-0.99).

Subgroup analysis

There were three studies with reported results concerning Gd-EOB-MRI for diagnostic performance of sub-centimeter HCC (≤ 1.0 cm)[17,18,21]. For the sub-centimeter HCC subgroup, pooled sensitivity and specificity were 0.69 (95%CI: 0.59-0.78) and 0.94 (95%CI: 0.88-0.98), respectively. Sensitivity for sub-centimeter lesions (0.69) was relatively low than values obtained for all small HCCs (0.91).

Comparison against Gd-EOB-MRI combined with DWI

Gd-EOB-MRI used alone and in combination with DWI were compared for performance by analyzing 3 studies that employed these diagnostic methods for the same patients[18,21,29]. The results suggested that Gd-EOB-MRI combined DWI was more sensitive compared with Gd-EOB-MRI alone, whether for small HCC or sub-centimeter lesions (Table 1).

Heterogeneity and meta-regression analysis

The heterogeneity of sensitivity and specificity tests was highly significant (P < 0.05 and I^2 > 75%) (Figure 4). This was strong evidence of between-study heterogeneity. Sensitivity and specificity for Gd-EOB-MRI were plotted on an ROC plane, and no curvilinear pattern was found. In addition, Spearman correlation coefficient (between the logit of sensitivity and that of specificity) for Gd-EOB-MRI was 0.237, with a P value of 0.51. No threshold effect was found in this meta-analysis. Meta-regression analysis showed that study design contributed significantly to heterogeneity (P = 0.04). However, other factors did not significantly contribute to study heterogeneity (P > 0.05).

DISCUSSION

Our results confirmed that Gd-EOB-MRI accurately detects small HCC. Previous reports showed that most HCCs appear as relatively low signal intensity lesions in HBP imaging because of inexistent gadoxetic acid uptake. Therefore, gadoxetic acid is expected to

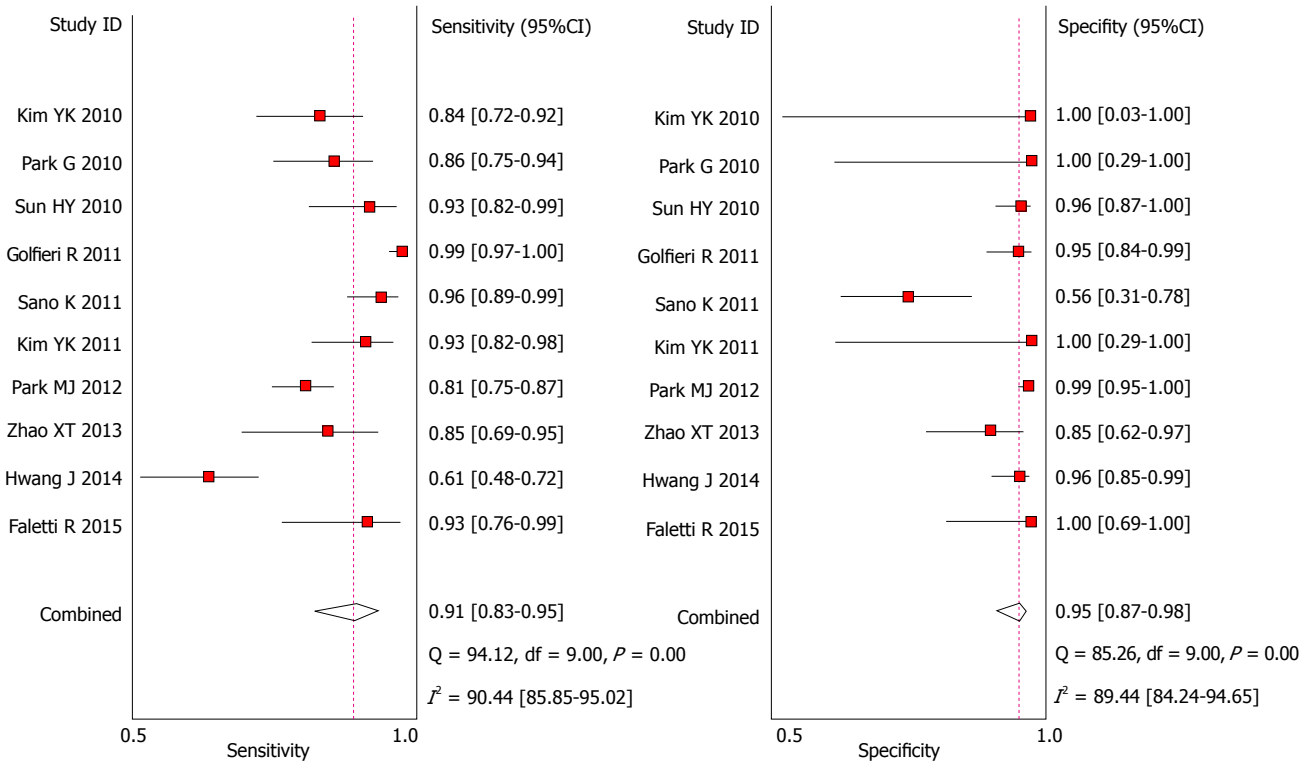

Figure 4 Forest plot of pooled sensitivity and specificity of gadoxetic acid-enhanced magnetic resonance imaging in detecting small hepatocellular carcinoma among patients with chronic liver disease. Summary sensitivity and specificity were 0.91 (95%CI: 0.83-0.95) and 0.95 (95%CI: 0.87-0.98), respectively.

Table 1 Comparison of the diagnostic performance of Gadoxetic acid-enhanced magnetic resonance imaging alone and combined with diffusion weighted imaging[1]

Diagnostic methods compared	Lesion size	Ref.	Summary sensitivity, % (95%CI)	Summary specificity, % (95%CI)
Gd-EOB-DTPA MRI alone	≤ 2.0 cm	[18,21,28]	0.77 (0.71-0.82)	0.97 (0.93-0.99)
Combined Gd-EOB-DTPA MRI with DWI			0.86 (0.82-0.90)	0.92 (0.88-0.96)
P value			0.0047	0.975
Gd-EOB-DTPA MRI alone	≤ 1.0 cm	[18,21]	0.56 (0.45-0.69)	0.96 (0.90-0.99)
Combined Gd-EOB-DTPA MRI with DWI			0.80 (0.68-0.88)	0.94 (0.87-0.98)
P value			0.0013	0.709

[1]The diagnostic performance of each modality was compared by using the *Z* test for Summary sensitivity and specificity, $P < 0.05$ was considered indicative of a statistically significant difference. Gd-EOB-MRI: Gadoxetic acid-enhanced MRI; DWI: Diffusion-weighted imaging.

enable excellent lesion detection and characterization for both hypervascular and hypovascular HCCs by arterial phase and HBP imaging, respectively[11,14,16,17,30]. Several studies suggested that hypointensity in HBP imaging, even in the absence of arterial phase hyperenhancement, is highly predictive of pre-malignant or malignant lesions[7,9,20]. Furthermore, early HCC is essentially hypovascular, with no dominant arterial blood supply. It is not surprising that conventional arterial phase imaging techniques are inefficient in evaluating early HCCs, with Gd-EOB-MRI HBP imaging being the only technique that successfully depicts early HCCs[19]. Previous findings confirmed that arterial hypervascularization delineation in HCC by gadoxetic acid is comparable to that by conventional Gd-DTPA[9]. Furthermore, sensitivity for hypervascular HCC detection is sufficiently high, and HBP images provide an added value to sensitivity, when Gd-EOB-MRI is applied[9,17,19]. However, previous studies found that HBP imaging is almost the only technique that successfully depicts hypovascular HCCs[17,19]. Dynamic contrast-enhanced MRI reveals hypervascular HCCs based on altered arterial vascularity due to the development of unpaired arteries and sinusoidal capillarisation[31]. A pathological explanation of arterial enhancement absence is the weak development of nontriadal arteries in hypovascular nodules (including early HCC), which make their characterization based on dynamic MR phases impossible[3,4,32]. However, hypovascular nodules usually show organic anion-transporting polypeptide under-expression, which begins prior to changes in hemodynamics. Therefore, they appear hypointense in HBP images[33].

We hypothesized that Gd-EOB-MRI and DWI combination has superior diagnostic performance over Gd-EOB-MRI alone, as it provides multi-parametric data

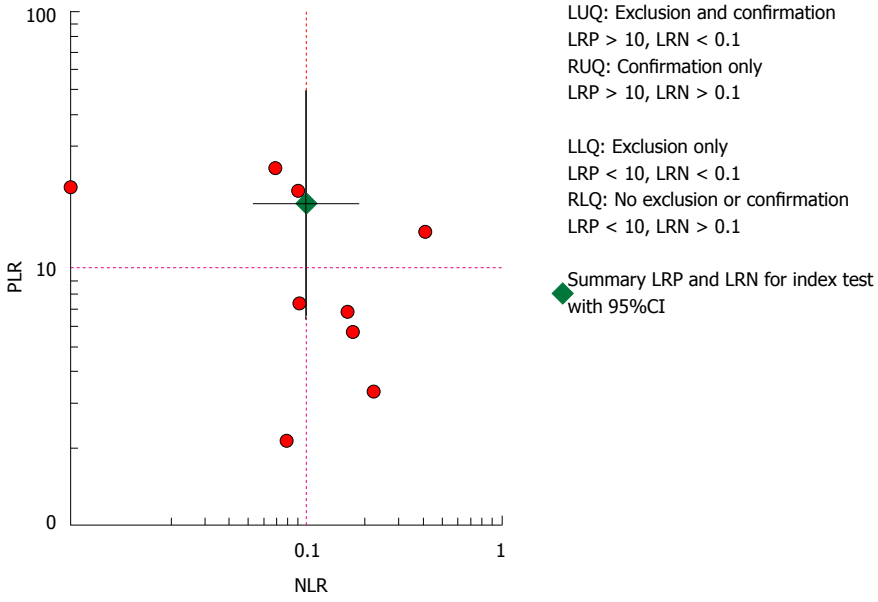

Figure 5 Scattergram of positive likelihood ratio and negative likelihood ratio. Pooled estimates for gadoxetic acid-enhanced MRI in the detection of small HCC were: PLR of 18.1 (95%CI: 6.6-49.4) and NLR of 0.10 (95%CI: 0.05-0.19). PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

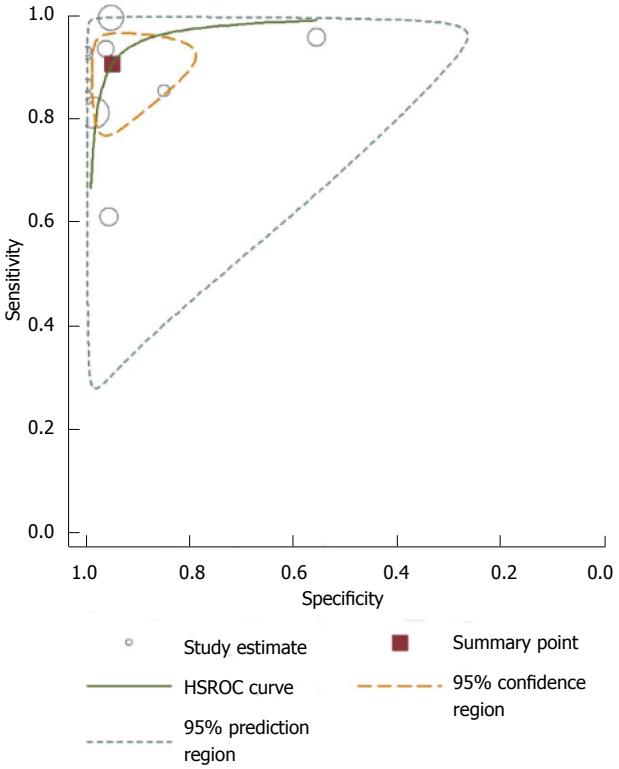

Figure 6 Hierarchical summary receiver operating characteristic plot of per-lesion diagnostic accuracy for gadoxetic acid-enhanced magnetic resonance imaging detection of small hepatocellular carcinoma in patients with chronic liver disease for the 10 included studies. The 95% confidence region and 95% prediction region around the pooled estimates illustrate the precision with which the pooled values were estimated (confidence ellipse of a mean) and to show the extent of between-study variation (prediction ellipse; likely range of values for a new study). HSROC: Hierarchical summary receiver operator characteristic.

such as vascular changes, hepatocyte function and cellular density[20,21,34]. In addition, given the importance of HBP imaging in the detection of small hypovascular HCCs, a considerable number of small HCCs are easily overlooked in the HBP set, particularly the lesions located adjacent to vessels. Thus, hyperintensity on DWI could contribute to improving the detection of small HCCs by helping reduce the number of mischaracterized lesions and allowing more accurate characterization of equivocal lesions[16,18,20,21].

With regard to tumor size in HCC, confident diagnosis of HCC in sub-centimeter hepatic nodules has been considered unfeasible[14,35]. Although per-lesion sensitivity estimates for MR imaging in sub-centimeter HCCs may be further increased with Gd-EOB-DTPA use, it is still relatively low[18,21]. The results of this meta-analysis showed the relatively low per-lesion sensitivity estimates for sub-centimeter HCCs. One possible explanation is that HBP ability to detect malignancies might be reduced in decompensated cirrhosis because gadoxetic acid uptake and metabolism are related to hepatocyte function. Previous studies showed a trend toward decreased sensitivity of Gd-EOB-MRI for detecting small HCC with increasing cirrhosis severity[21,36]. It is clear that a cirrhotic liver shows restricted diffusion in line with hepatic fibrosis severity[37]. Thus, it remains difficult to identify HCC in severely cirrhotic liver in any imaging studies; this limits the usefulness of both Gd-EOB-MRI and DWI in patients with decompensated liver cirrhosis[18,20,21,36], especially for sub-centimeter HCCs.

Investigation of reasons for heterogeneity rather than computation of a single summary measure is an important purpose of meta-analysis[38]. Significant heterogeneity was found in pooled analysis of the included 10 studies. Spearman correlation analysis demonstrated there was no significant threshold effect. This work suggested that study design may affect diagnostic accuracy. These findings corroborated a recently published report[39], which showed that case series studies have significantly higher per-lesion sensitivity than case-control studies. Therefore, it is important that

future studies adopt study designs that better control biases and provide higher levels of evidence such as cohort studies and randomized controlled trials.

In seven previous meta-analyses[40-46], investigators evaluated the detection of HCC of any size by Gd-EOB-DTPA, three of which yielded a subgroup analysis for small HCCs[40-42]. In a recent meta-analysis, Kierans *et al*[47] evaluated the diagnostic performance of dynamic contrast-enhanced MRI for the detection of small HCC with subgroup analysis of Gd-EOB-MRI, whose results were consistent with our findings[40-42,47]. However, compared with the above reports, this study has the following characteristics: All cases in the included literatures had a history of chronic liver disease; subgroup analysis for the diagnostic performance of Gd-EOB-MRI and DWI combination in the detection of sub-centimeter HCC was performed. In addition, in two recent meta-analyses[39,48], investigators compared the diagnostic performance of ultrasonography, CT and MRI in the detection of HCC of any size without subgroup analysis. Therefore, in comparison with the above previous meta-analyses, we expanded the evaluation to combined Gd-EOB-MRI and DWI, and detectability for sub-centimeter HCC.

Our meta-analysis has several limitations. First, data were collected in a prospective manner, with a limited number of studies (only three studies), which resulted in a major methodologic limitation of including many studies with retrospective patient data collection. Pooling such suboptimal retrospective results may have caused a bias toward increased diagnostic sensitivity[49]. Second, participants in included studies were both patients diagnosed with HCC based on findings prior imaging tests or other clinical data and those suspected of having HCC, which might have caused selection bias. In addition, limited numbers of lesions were diagnosed during liver transplantation (only two studies), which might have resulted in an overestimation of the diagnostic performance of Gd-EOB-MRI by decreasing the number of false-negative lesions. Finally, considerable heterogeneity was observed with per-lesion analysis. For example, whether or not interpretation of pathology data was blinded from Gd-EOB-MRI seemed to be a common weakness, and only 4 studies used the same reference standard. Furthermore, we found substantial variation in the way Gd-EOB-MRI findings were used for the identification of HCC, indicating a lack of consensus regarding diagnostic criteria and thresholds. To overcome the heterogeneity of the present data, we used both the hierarchical summary ROC model and the random-effects model. Because the 95%CIs were not substantially wide, we believe that the present results are valuable. However, heterogeneity in this type of diagnostic study remains a point of concern.

In conclusion, our meta-analysis showed that Gd-EOB-MRI has good diagnostic performance in the detection of small HCC (≤ 2.0 cm) among patients with chronic liver disease, but relatively lower performance for the detection of sub-centimeter HCC (≤ 1.0 cm). Combination of Gd-EOB-MRI and DWI can improve the diagnostic sensitivity of MRI for the detection of small HCC.

COMMENTS

Background

In recent years, gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI) has shown that hepatobiliary phase imaging provides improvement in the diagnosis of small hepatocellular carcinoma (HCC ≤ 2.0 cm). However, the results are limited thus far by small numbers of included patients with chronic liver disease, especially for sub-centimeter lesions (≤ 1.0 cm). In addition, no consensus is available regarding diagnostic performance of combined Gd-EOB-MRI and diffusion weighted imaging (DWI) in the detection of small HCC.

Research frontiers

Despite important advances in multidisciplinary therapies, complete curative treatment of early-stage small HCC remains the only option for long-term patient survival. Thus, the importance of early detection of HCC has been emphasized, especially with the application of noninvasive multi-modality imaging.

Innovations and breakthroughs

In this study, the authors investigated the value of Gd-EOB-MRI for the diagnosis of sub-centimeter HCC. It is also believed to be the first meta-analysis evaluating combined Gd-EOB-MRI and DWI in the detection of small HCC.

Applications

This meta-analysis showed that Gd-EOB-MRI has relatively lower performance for the detection of sub-centimeter HCC, and combination of Gd-EOB-MRI and DWI can improve diagnostic sensitivity. In clinical practice, the addition of DWI to routine protocol of Gd-EOB-MRI may help increase sensitivity in the detection of small HCC, especially for sub-centimeter lesion.

Peer-review

This is a meta-analysis evaluating Gd-EOB-MRI for the detection of small HCC in patients with chronic liver disease, showing that Gd-EOB-MRI has good diagnostic performance for the detection of small HCC; in addition, Gd-EOB-MRI and DWI combination improves the diagnostic sensitivity of MRI for detecting small HCC. The methods used in this study are state of the art, and data are well presented and discussed in the light of the current literature.

REFERENCES

1 **Bosch FX**, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; **127**: S5-S16 [PMID: 15508102 DOI: 10.1053/j.gastro.2004.09.011]

2 **Rosencher N**, Vassilieff N, Guigonis V, Toulon P, Conseiller C. Comparison of effects of Elohes and albumin on hemostasis in orthopedic surgery. *Ann Fr Anesth Reanim* 1992; **11**: 526-530 [PMID: 1476283 DOI: 10.1002/lt.20042]

3 **International Consensus Group for Hepatocellular Neoplasia**. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009; **49**: 658-664 [PMID: 19177576 DOI: 10.1002/hep.22709]

4 **Desmet VJ**. East-West pathology agreement on precancerous liver lesions and early hepatocellular carcinoma. *Hepatology* 2009; **49**: 355-357 [PMID: 19127518 DOI: 10.1002/hep.22681]

5 **Nakashima Y**, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M. Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. *Hepatol Res* 2003; **26**: 142-147 [PMID: 12809942 DOI: 10.1016/S1386-

6346(03)00007-X]
6 **Sala M**, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352-1360 [PMID: 15565564 DOI: 10.1002/hep.20465]
7 **Zech CJ**, Bartolozzi C, Bioulac-Sage P, Chow PK, Forner A, Grazioli L, Huppertz A, Laumonier H, Min Lee J, Murakami T, Ricke J, Sirlin CB. Consensus report of the Fifth International Forum for Liver MRI. *AJR Am J Roentgenol* 2013; **201**: 97-107 [PMID: 23789662 DOI: 10.2214/AJR.12.9491]
8 **Bolondi L**, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, Venturi AM, Piscaglia F. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology* 2005; **42**: 27-34 [PMID: 15954118 DOI: 10.1002/hep.20728]
9 **Park G**, Kim YK, Kim CS, Yu HC, Hwang SB. Diagnostic efficacy of gadoxetic acid-enhanced MRI in the detection of hepatocellular carcinomas: comparison with gadopentetate dimeglumine. *Br J Radiol* 2010; **83**: 1010-1016 [PMID: 20682591 DOI: 10.1259/bjr/66686028]
10 **Kim YK**, Kim CS, Han YM, Park G. Detection of small hepatocellular carcinoma: can gadoxetic acid-enhanced magnetic resonance imaging replace combining gadopentetate dimeglumine-enhanced and superparamagnetic iron oxide-enhanced magnetic resonance imaging? *Invest Radiol* 2010; **45**: 740-746 [PMID: 20644488 DOI: 10.1097/RLI.0b013e3181e943a7]
11 **Sun HY**, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, Han JK, Choi BI. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (& lt; or =2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. *Invest Radiol* 2010; **45**: 96-103 [PMID: 20057319 DOI: 10.1097/RLI.0b013e3181c5faf7]
12 **Yoon SH**, Lee JM, So YH, Hong SH, Kim SJ, Han JK, Choi BI. Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3 cm in diameter: tumor size and cellular differentiation. *AJR Am J Roentgenol* 2009; **193**: W482-W489 [PMID: 19933622 DOI: 10.2214/AJR.08.1818]
13 **Park MJ**, Kim YS, Lee WJ, Lim HK, Rhim H, Lee J. Outcomes of follow-up CT for small (5-10-mm) arterially enhancing nodules in the liver and risk factors for developing hepatocellular carcinoma in a surveillance population. *Eur Radiol* 2010; **20**: 2397-2404 [PMID: 20559837 DOI: 10.1007/s00330-010-1810-y]
14 **Forner A**, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Brú C, Bruix J. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008; **47**: 97-104 [PMID: 18069697]
15 **Hwang J**, Kim SH, Lee MW, Lee JY. Small (≤ 2 cm) hepatocellular carcinoma in patients with chronic liver disease: comparison of gadoxetic acid-enhanced 3.0 T MRI and multiphasic 64-multirow detector CT. *Br J Radiol* 2012; **85**: e314-e322 [PMID: 22167508 DOI: 10.1259/bjr/27727228]
16 **Park MJ**, Kim YK, Lee MH, Lee JH. Validation of diagnostic criteria using gadoxetic acid-enhanced and diffusion-weighted MR imaging for small hepatocellular carcinoma (and lt; = 2.0 cm) in patients with hepatitis-induced liver cirrhosis. *Acta Radiol* 2013; **54**: 127-136 [PMID: 23148300 DOI: 10.1258/ar.2012.120262]
17 **Golfieri R**, Renzulli M, Lucidi V, Corcioni B, Trevisani F, Bolondi L. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to Dynamic MRI in the detection of hypovascular small (≤ 2 cm) HCC in cirrhosis. *Eur Radiol* 2011; **21**: 1233-1242 [PMID: 21293864 DOI: 10.1007/s00330-010-2030-1]
18 **Park MJ**, Kim YK, Lee MW, Lee WJ, Kim YS, Kim SH, Choi D, Rhim H. Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. *Radiology* 2012; **264**: 761-770 [PMID: 22843769 DOI: 10.1148/radiol.12112517]
19 **Sano K**, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, Nakano M, Sakamoto M, Nakazawa T, Asakawa M, Fujii H, Kitamura T, Enomoto N, Araki T. Imaging study of early hepatocellular carcinoma: usefulness of gadoxetic acid-enhanced MR imaging. *Radiology* 2011; **261**: 834-844 [PMID: 21998047 DOI: 10.1148/radiol.11101840]
20 **Faletti R**, Cassinis MC, Fonio P, Bergamasco L, Pavan LJ, Rapellino A, David E, Gandini G. Multiparametric Gd-EOB-DTPA magnetic resonance in diagnosis of HCC: dynamic study, hepatobiliary phase, and diffusion-weighted imaging compared to histology after orthotopic liver transplantation. *Abdom Imaging* 2015; **40**: 46-55 [PMID: 24965896 DOI: 10.1007/s00261-014-0180-3]
21 **Hwang J**, Kim YK, Kim JM, Lee WJ, Choi D, Hong SS. Pretransplant diagnosis of hepatocellular carcinoma by gadoxetic acid-enhanced and diffusion-weighted magnetic resonance imaging. *Liver Transpl* 2014; **20**: 1436-1446 [PMID: 25103727 DOI: 10.1002/lt.23974]
22 **Yu MH**, Kim JH, Yoon JH, Kim HC, Chung JW, Han JK, Choi BI. Small (≤1-cm) hepatocellular carcinoma: diagnostic performance and imaging features at gadoxetic acid-enhanced MR imaging. *Radiology* 2014; **271**: 748-760 [PMID: 24588677 DOI: 10.1148/radiol.14131996]
23 **Whiting PF**, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529-536 [PMID: 22007046 DOI: 10.7326/0003-4819-155-8-201110180-00009]
24 **Harbord RM**, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007; **8**: 239-251 [PMID: 16698768 DOI: 10.1093/biostatistics/kxl004]
25 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]
26 **Leeflang MM**, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008; **149**: 889-897 [PMID: 19075208 DOI: 10.7326/0003-4819-149-12-200812160-00008]
27 **Deeks JJ**, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005; **58**: 882-893 [PMID: 16085191]
28 **Kim YK**, Kim CS, Han YM, Yu HC, Choi D. Detection of small hepatocellular carcinoma: intraindividual comparison of gadoxetic acid-enhanced MRI at 3.0 and 1.5 T. *Invest Radiol* 2011; **46**: 383-389 [PMID: 21467946 DOI: 10.1097/RLI.0b013e318217b8fb]
29 **Zhao XT**, Li WX, Chai WM, Chen KM. Detection of small hepatocellular carcinoma using gadoxetic acid-enhanced MRI: Is the addition of diffusion-weighted MRI at 3.0T beneficial? *J Dig Dis* 2014; **15**: 137-145 [PMID: 24354621 DOI: 10.1111/1751-2980.12119]
30 **Ichikawa T**, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, Kamura T, Gabata T, Murakami T, Ito K, Hirohashi S, Nishie A, Saito Y, Onaya H, Kuwatsuru R, Morimoto A, Ueda K, Kurauchi M, Breuer J. Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. *Invest Radiol* 2010; **45**: 133-141 [PMID: 20098330 DOI: 10.1097/RLI.0b013e3181caea5b]
31 **Morinaga S**, Imada T, Shimizu A, Akaike M, Sugimasa Y, Takemiya S, Takanashi Y. Angiogenesis in hepatocellular carcinoma as evaluated by alpha smooth muscle actin immunohistochemistry. *Hepatogastroenterology* 2001; **48**: 224-228 [PMID: 11268971]
32 **Kogita S**, Imai Y, Okada M, Kim T, Onishi H, Takamura M, Fukuda K, Igura T, Sawai Y, Morimoto O, Hori M, Nagano H, Wakasa K, Hayashi N, Murakami T. Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. *Eur Radiol* 2010; **20**: 2405-2413 [PMID: 20490505 DOI: 10.1007/s00330-010-1812-9]
33 **Kitao A**, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, Kozaka K, Yoneda N, Yamashita T, Kaneko S, Nakanuma Y. Hepatocellular carcinoma: signal intensity at gadoxetic acid-

enhanced MR Imaging--correlation with molecular transporters and histopathologic features. *Radiology* 2010; **256**: 817-826 [PMID: 20663969 DOI: 10.1148/radiol.10092214]

34 **Kim JE**, Kim SH, Lee SJ, Rhim H. Hypervascular hepatocellular carcinoma 1 cm or smaller in patients with chronic liver disease: characterization with gadoxetic acid-enhanced MRI that includes diffusion-weighted imaging. *AJR Am J Roentgenol* 2011; **196**: W758-W765 [PMID: 21606265 DOI: 10.2214/AJR.10.4394]

35 **Sangiovanni A**, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, Massironi S, Della Corte C, Ronchi G, Rumi MG, Biondetti P, Colombo M. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 2010; **59**: 638-644 [PMID: 19951909 DOI: 10.1136/gut.2009.187286]

36 **Kim AY**, Kim YK, Lee MW, Park MJ, Hwang J, Lee MH, Lee JW. Detection of hepatocellular carcinoma in gadoxetic acid-enhanced MRI and diffusion-weighted MRI with respect to the severity of liver cirrhosis. *Acta Radiol* 2012; **53**: 830-838 [PMID: 22847903 DOI: 10.1258/ar.2012.120099]

37 **Sandrasegaran K**, Akisik FM, Lin C, Tahir B, Rajan J, Saxena R, Aisen AM. Value of diffusion-weighted MRI for assessing liver fibrosis and cirrhosis. *AJR Am J Roentgenol* 2009; **193**: 1556-1560 [PMID: 19933647 DOI: 10.2214/AJR.09.2436]

38 **Petitti DB**. Approaches to heterogeneity in meta-analysis. *Stat Med* 2001; **20**: 3625-3633 [PMID: 11746342]

39 **Lee YJ**, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, Han JK, Choi BI. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. *Radiology* 2015; **275**: 97-109 [PMID: 25559230 DOI: 10.1148/radiol.14140690]

40 **Liu X**, Zou L, Liu F, Zhou Y, Song B. Gadoxetic acid disodium-enhanced magnetic resonance imaging for the detection of hepatocellular carcinoma: a meta-analysis. *PLoS One* 2013; **8**: e70896 [PMID: 23967130]

41 **Chen L**, Zhang L, Bao J, Zhang J, Li C, Xia Y, Huang X, Wang J. Comparison of MRI with liver-specific contrast agents and multidetector row CT for the detection of hepatocellular carcinoma: a meta-analysis of 15 direct comparative studies. *Gut* 2013; **62**: 1520-1521 [PMID: 23929696 DOI: 10.1136/gutjnl-2013-305231]

42 **Wu LM**, Xu JR, Gu HY, Hua J, Chen J, Zhu J, Zhang W, Hu J. Is liver-specific gadoxetic acid-enhanced magnetic resonance imaging a reliable tool for detection of hepatocellular carcinoma in patients with chronic liver disease? *Dig Dis Sci* 2013; **58**: 3313-3325 [PMID: 23884757 DOI: 10.1007/s10620-013-2790-y]

43 **Li X**, Li C, Wang R, Ren J, Yang J, Zhang Y. Combined Application of Gadoxetic Acid Disodium-Enhanced Magnetic Resonance Imaging (MRI) and Diffusion-Weighted Imaging (DWI) in the Diagnosis of Chronic Liver Disease-Induced Hepatocellular Carcinoma: A Meta-Analysis. *PLoS One* 2015; **10**: e0144247 [PMID: 26629904 DOI: 10.1371/journal.pone.0144247]

44 **Ye F**, Liu J, Ouyang H. Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid (Gd-EOB-DTPA)-Enhanced Magnetic Resonance Imaging and Multidetector-Row Computed Tomography for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *Medicine* (Baltimore) 2015; **94**: e1157 [PMID: 26266348 DOI: 10.1097/MD.0000000000001157]

45 **Junqiang L**, Yinzhong W, Li Z, Shunlin G, Xiaohui W, Yanan Z, Kehu Y. Gadoxetic acid disodium (Gd-EOBDTPA)-enhanced magnetic resonance imaging for the detection of hepatocellular carcinoma: a meta-analysis. *J Magn Reson Imaging* 2014; **39**: 1079-1087 [PMID: 25006627]

46 **Chen L**, Zhang L, Liang M, Bao J, Zhang J, Xia Y, Huang X, Wang J. Magnetic resonance imaging with gadoxetic acid disodium for the detection of hepatocellular carcinoma: a meta-analysis of 18 studies. *Acad Radiol* 2014; **21**: 1603-1613 [PMID: 25262955 DOI: 10.1016/j.acra.2014.08.003]

47 **Kierans AS**, Kang SK, Rosenkrantz AB. The Diagnostic Performance of Dynamic Contrast-enhanced MR Imaging for Detection of Small Hepatocellular Carcinoma Measuring Up to 2 cm: A Meta-Analysis. *Radiology* 2016; **278**: 82-94 [PMID: 26098460 DOI: 10.1148/radiol.2015150177]

48 **Chou R**, Cuevas C, Fu R, Devine B, Wasson N, Ginsburg A, Zakher B, Pappas M, Graham E, Sullivan SD. Imaging Techniques for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015; **162**: 697-711 [PMID: 25984845 DOI: 10.7326/M14-2509]

49 **Deeks J**. Systematic reviews of evaluations of diagnostic and screening tests. In: Egger M, Smith GD, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. 2nd ed. London, England: BMJ Books, 2001: 248-282

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Isolated hepatic perfusion for unresectable hepatic malignancies: A systematic review and meta-analysis

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Abstract

AIM

To investigate the efficacy and safety of isolated hepatic perfusion (IHP) in the management of unresectable liver malignancies.

METHODS

Studies were identified manually and on-line by using PubMed and EMBASE database. We formulate the eligibility criteria according to the PICOS elements, and accessed the quality of studies using the MINORS instrument. Data from all included studies were carefully investigated. We calculated the pooled response rate and incidences of mortality reported from all eligible studies by using the Meta-Analyst software, and we computed a pooled relative risk (RR) and 95%CI by using the Comprehensive Meta-Analysis software. Heterogeneity was quantified evaluated using I^2 statistic.

RESULTS

Eight studies, including 502 patients, were selected. Of these, six studies performed IHP, while the other two studies performed percutaneous IHP. The results showed that the pooled response rate was 60.8% (95%CI: 53.1%-68%), I^2 = 37.1%. The median overall survival was 20 mo (range: 12.1 to 25 mo) following IHP or PIHP. The pooled mortality rate was 5.4% (95%CI: 2.5%-11.2%), I^2 = 37.5%. Prognostic factors predict the response to IHP or survival, and were reported in six studies. Meta-analysis demonstrated that Gender was not associated with overall survival (RR = 0.877, 95%CI: 0.564-1.365); however, carcino-embryonic antigen $\leqslant$ 30 ng/mL was associated with a significant improvement in survival outcomes with colorectal cancer patients (RR = 2.082, 95%CI: 1.371-3.163), and there was no significant heterogeneity.

CONCLUSION

The present systemic review and meta-analysis suggest that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary

malignancies.

Key words: Isolated hepatic perfusion; Unresectable; Hepatic malignancy; Systematic review; Meta-analysis

Core tip: The treatment of unresectable liver malignancies is an important and difficult clinical problem. Many studies suggested that isolated hepatic perfusion to be efficacious and safe in the management of unresectable liver malignancies. However, there has not yet been a systematic analysis to evaluate this method. Therefore we reviewed all the literature we could get and conducted a systemic review. In the present systemic review we demonstrated all details and results of this technique in every aspect and intensively investigated these data, so that it will help readers to understand this technique in a quick, comprehensive and objective way.

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INTRODUCTION

Liver metastases are frequent manifestations of a variety of malignancies and are often the cause of mortality. The optimal curative treatment of primary or secondary liver tumors is surgical resection. However, less than one third of cases with malignant liver tumors are candidates for surgical intervention, whereas the rest exhibit unresectable feature due to the degree of liver involvement, insufficient liver remnant, or medical comorbidity[1,2]. For these patients, conventional chemotherapy may be applied systemically but with little benefit and substantial toxicity.

Isolated hepatic perfusion (IHP) was developed over the past several decades as a complex open surgical technique to isolate the liver and perfuse the entire organ with high dosage chemotherapy. The complete vascular isolation and mobilization of liver allow maximal anti-tumor effect as well as minimal systemic toxicity[3,4]. As an alternative approach of IHP, percutaneous IHP (PIHP) obviate a large abdominal operation, and allows repeatable manipulation, which may enable the patients to get maximized therapeutic effects while having a faster recovery.

The management of patients with unresectable hepatic malignancies is a significant clinical problem. There are many uncertainties and controversies in treating these patients using either systemic or different regional therapies. Here we conduct this present study to systematically evaluate the existing literature of IHP and PIHP with specific focus on the profiles of efficacy, safety, and survival benefit.

MATERIALS AND METHODS

Literature search strategy

Studies were identified from the Pubmed and EMBASE electronic databases through January 2016 for relevant studies, using a combined MeSH terms and keywords search strategy. The following search terms were used: "isolated hepatic perfusion", "tumor", "cancer", "neoplasm", "carcinoma", "metastases", "nonresectable". These themes were combined using the Boolean operator "AND", "OR" in several combinations without restrictions. Articles were assessed based on the inclusion and exclusion criteria. We also reviewed the reference lists of retrieved papers and recent reviews.

Selection criteria

We attempted to formulate the eligibility criteria according to the PICOS elements. We performed an initial screening of titles or abstracts, and a second screening was based on full-text review. Studies were considered eligible if they met the following criteria: (1) Patients with unresectable primary or secondary liver malignancies; (2) Studies using IHP or PIHP will be included. Variations in drug, dosage, timing, frequency and duration will be tolerated; (3) Studies reporting one or more of these outcomes are eligible: The therapeutic response, toxicity, survival and prognostic factors; (4) Clinical trials and prospective cohort studies, with patients who underwent IHP or PIHP $\geqslant$ 25. If there were multiple articles based on the same sample, the one that reported the most detailed data will be included. If multiple publications from the same institution were identified, the most resent update with the largest number of patients will be included.

Quality assessments

We accessed the quality of studies using the MINORS instrument[5]. Quality assessment was carried out independently by two reviewers. If both reviewers agreed, the study could be included to the systematic review. Discrepancies were in consultation with the senior author. The deviations between these included studies were taken into account during the quality assessment stage.

Data extraction

The data from all included studies were clearly tabulated. Information collected from these studies included study characteristics, patient and disease characteristics, parameters of IHP treatment, response rate, morbidity and mortality, survival information and prognostic factors.

Statistical analysis

We used a published analysis technique[6] to calculate

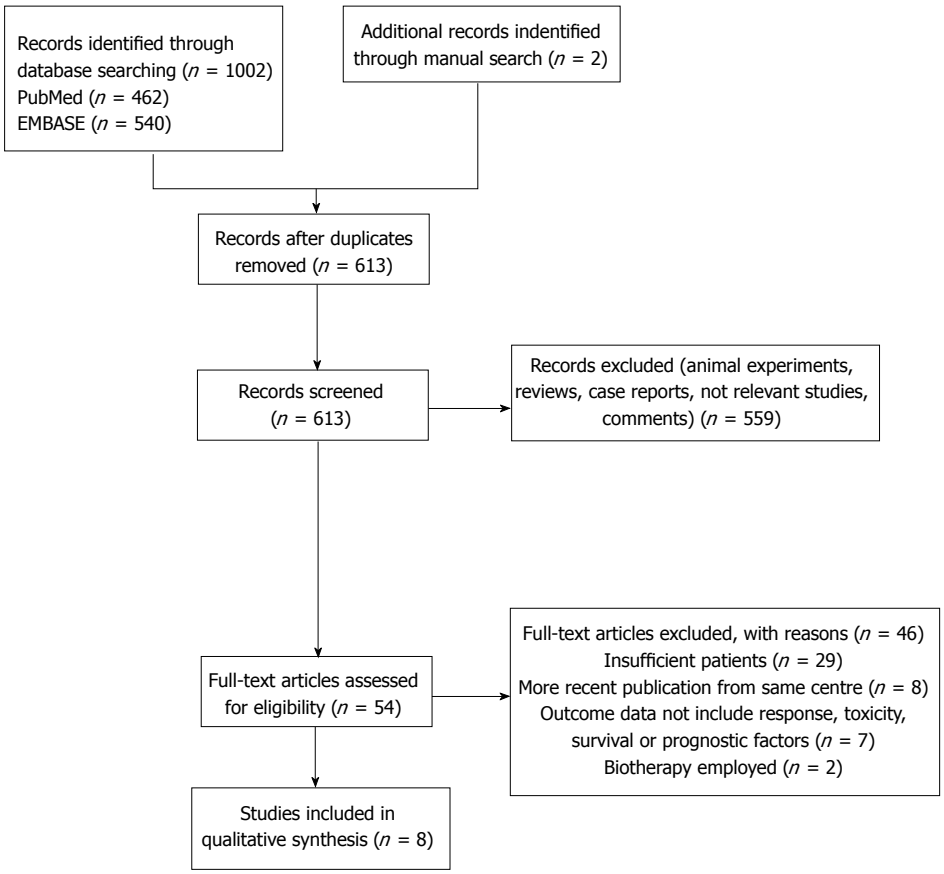

Figure 1 Literature search PRIMSA flow diagram.

the pooled response rate and incidences of mortality reported from all eligible studies by using the Meta-Analyst software (version Beta 3.13, Tufts Medical Center). And we computed a pooled relative risk (RR) and 95%CI by using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey). Heterogeneity was quantified evaluated using I^2 statistic. I^2 value of lower than 50% manifested with no or moderate heterogeneity, whereas I^2 value of greater than 50% was represented with large or extreme heterogeneity[7]. The random effects model was used when heterogeneity existed.

RESULTS

Identification of eligible studies

The process of identifying eligible studies is summarized by the PRISMA chart[8] in Figure 1. We initially retrieved 1002 articles from the PubMed and EMBASE database and two further articles were yielded through manual search of reference lists. After the removal of duplicates, 613 unique citations were identified. Of these, the majority was excluded after screening on titles or abstracts, mainly because they were animal experiments, reviews, case reports or not relevant to our analysis. Fifty-four full-text articles were intensively reviewed. Twenty-nine studies were considered to have low volume patients (< 25)[9-37]. Seven articles did not assess for response, toxicity, survival or prognostic factors[38-44]. Two studies employed biotherapy[45,46], and eight articles were excluded due to more publication from the same center or based on the same cohort[47-54]. The remaining eight articles were included[55-62]. The characteristics of included studies are summarized in Table 1.

Patient demographics and disease characteristics

The patient and disease characteristics are summarized in Table 2. Eight studies including a total of 502 patients were reviewed. Except one article that did not report the sex ratio, the rate of male *vs* female reported by other studies was 1.23:1. The majority of patients had unresectable colorectal origin liver metastasis (56%) or melanoma (27%). Other pathology causing liver malignancies include hepatocellular carcinoma (14%), cholangiocarcinoma (0.6%), neuroendocrine neoplasms (0.8%), breast cancer (0.4%), renal cell carcinoma (0.4%), pancreatic adenocarcinoma (0.2%), appendiceal cancer (0.2%), adrenal adenocarcinoma (0.2%), retroperitoneal sarcoma (0.2%), *etc.* All the included studies had reported the eligibility criteria for patients, including patients who had unresectable, biopsy-proven hepatic malignancies, Eastern Cooperative Oncology Group performance status of 0-1, and other criteria to

Table 1 Summary of data points presented in relevant clinical trials

Ref.	Year	Country	Research institution	Study period	MINORS score	IHP patients (*n*)	Tumor details	Eligibility and exclusion criteria	IHP details and response rate	Morbidity and mortality	Compli-cations and toxicities	Long-term survival	Prognostic factors
Olofsson *et al*[55]	2014	Sweden	The Swedish National Board of Health and Welfare	April 2005 to March 2011	18	34	Y	Y	Y	Y	Y	Y	Y
Magge *et al*[56]	2014	United States	University of Pittsburgh Cancer Institute	November 2003 to February 2012	12	91	Y	NR	Y	Y	Y	Y	Y
Fukumoto *et al*[57]	2014	Japan	The Kobe University Hospital	January 1989 to December 2010	12	68	Y	Y	Y	NR	Y	Y	Y
Alexander *et al*[58]	2009	United States	NCI	June 1994 to July 2005	12	120	Y	Y	Y	Y	Y	Y	Y
van Iersel *et al*[59]	2008	Nether-lands	Leiden University Medical Center	August 1994 to December 2004	12	105	Y	Y	Y	Y	Y	Y	Y
Rizell *et al*[60]	2008	Sweden	Sahlgrenska University Hospital	1985 to 2007	11	27	Y	Y	Y	Y	Y	Y	NR
Pingpank *et al*[61]	2005	United States	NCI	July 2001 to January 2004	12	28	Y	Y	Y	Y	Y	NR	NR
Alexander *et al*[62]	2003	United States	NCI	December 1997 to August 2002	12	29	Y	Y	Y	Y	Y	Y	Y

Y: Recorded data available; NR: Not reported; NCI: The National Cancer Institute; MINORS: Methodological index for non-randomized studies.

ensure that the patients would have good tolerance to the operation.

Isolated hepatic perfusion details and response

The isolated hepatic perfusion details and response rate are summarized in Table 3. Six of the eight studies performed IHP[55,56,58-60,62], while the other two studies performed PIHP[57,61]. Melphalan, TNF, or a combination of these two drugs was employed in most studies. The majority of studies reported to have a perfusion time of 60 min and the perfusate temperature was kept at 39.5 ℃-40 ℃. The pooled response rate was 60.8% (95%CI: 53.1%-68%), I^2 = 37.1% (Figure 2).

Morbidity and mortality

Toxicity, morbidity, and mortality are shown in Table 4. The pooled mortality rate was 5.4% (95%CI: 2.5%-11.2%), I^2 = 37.5% (Figure 3). The majority of studies reported a reversible hepatic toxicity, mainly manifested in transient elevations in transaminases and serum bilirubin, which return towards normal approximately by postoperative day 7. Besides hepatic toxicity, the most common hematologic toxicity was anemia, thrombocytopenia, and neutropenia. Significant nonhematologic complications were rare.

Survival outcomes

Seven studies had assessed the survival outcomes we listed in Table 5. Following IHP or PIHP, the median overall survival was reported in a range of 12.1 to 25 mo, with the median value to be 20 mo. There is one study using PIHP protocol that reported the median overall survival to be 25 mo, while that for patients who underwent IHP was 19 mo.

Prognostic factors

Prognostic factors predict the response to IHP or survival, and were reported in six studies (Table 6). Olofsson *et al*[55] found the volume of liver occupied with metastases (RR = 1.04, *P* = 0.02) and, the diameter of the largest metastasis (RR = 1.23, *P* = 0.01) to be significant for survival on univariate analysis. Magge *et al*[56] found that CRC patients who received FUDR within one year after IHP had better survival than those did not receive floxuridine (RR = 0.3, *P* = 0.043). Fukumoto *et al*[57] reported that tumor response to PIHP

Table 2 Patient demographics and disease characteristics

Ref.	Patients (*n*)	Age (median)	Male: Female	Primary tumor	Primary tumor treatment *n* (%)			Liver involvement *n* (%) or mean percentage (range)			Number of liver metastases	Largest liver metastases diameter (cm), median (range)	Extra-hepatic metastases *n* (%)
					Excision	Chemo-therapy	No treatment	< 5%	25%-0%	> 0%			
Olofsson *et al*[55]	34	61 (17-77)	15:19	Ocular melanoma	15 (44%)	19 (56%)	None	31 (91%)	3 (9%)	None	1-100 31 (91%) > 100 3(9%))	2.35 (1.0-6.4)	None
Magge *et al*[56]	91	54.3 (24-77)	50:41	CRC 54 (59.3%) Ocular melanoma 29 (32%) Others 8 (8.7%)	None	CRC 47 (87%)	44 (48%)	30% (5%-80%)			9 (2-105)	NR	NR
Fukumoto *et al*[57]	68	60 (52-67)	61:7	HCC	68 (100%)	NR	None	NR	NR	NR	⩾ 4	8.3 (5.0-12.6)	None
Alexander *et al*[58]	120	52 (22-74)	41:79	CRC	NR	NR	NR	20% (5%-75%)			NR	8 (1-50)	NR
Iersel *et al*[59]	105	⩽ 70	78:27	CRC	4 (3.8%)	51 (48.6%)	50 (47.6%)	NR	NR	NR	< 10 71 (68%) ⩾ 10 34 (32%)	NR	34 (32.4%)
Rizell *et al*[60]	27	53 (36-77)	NR	Melanoma	NR	NR	NR	6 (22%)	11 (41%)	10 (37%)	NR	NR	NR
Pingpank *et al*[61]	28	49 (17-74)	14:14	Melanoma 13 CRC 2 Others 13	NR	NR	NR	NR	NR	NR	NR	NR	8 (29%)
Alexander *et al*[62]	29	49 (26-73)	15:14	Ocular melanoma	NR	NR	NR	20 (69%)	8 (28%)	1 (3%)	25 (4 ⩾ 50)	5.6 (2-14)	NR

CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; NR: Not reported.

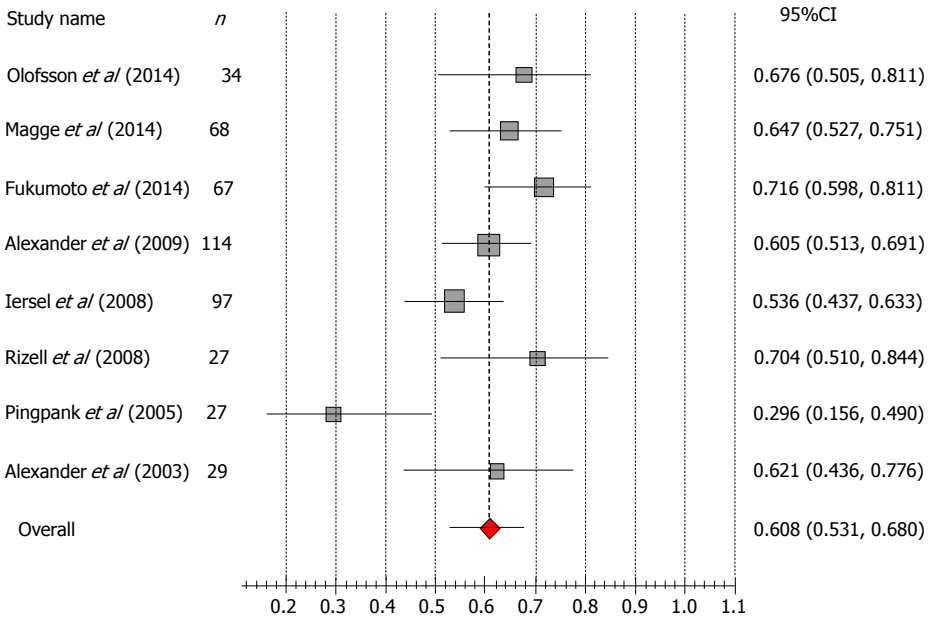

Figure 2 Forest plot of the studies for response rate. Pooled estimate (%) = 60.8%, 95%CI: 53.1%-68.0%, I^2 = 37.1%.

(RR = 0.108, P < 0.001) and normalization of serum des-γ-carboxy prothrombin (DCP) after PIHP (RR = 0.28, P < 0.001) were both independent prognostic factors in HCC patients for survival. In Alexander's study published in 2009, they carried out further research on prognostic factors. They found that patients who received IHP with postoperative hepatic arterial infusion chemotherapy with Floxuridine (FUDR) markedly

Table 3 Isolated hepatic perfusion details and response rate

Ref.	Patients evaluable for response (*n*)	IHP/ PIHP	IHP chemotherapy protocol					Patient response				Overall response (CR + PR, %)
			Drug	Dose	Perfusion temperature	Perfusion time	Courses per patient (*n*)	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)	
Olofsson *et al*[55]	34	IHP	Melphalan	1 mg/kg	40 ℃	60 min	1	4 (12%)	19 (56%)	6 (18%)	5 (15%)	68%
Magge *et al*[56]	68	IHP	Melphalan 1.5 mg/kg 40 mg/m^2 Oxaliplatin Oxaliplatin + 5FU 5FU 200 mg/m^2		40 ℃	60 min	1	44 (64.7%)		24 (35.3%)		64.7%
Fukumoto *et al*[57]	67	PIHP	Mitomycin C and/or Doxorubicin	20-40 mg/m^2 60-120 mg/m^2	NR	30-40 min	1.51 (range 1-3)	21 (31.3%)	27 (40.3%)	11 (16.4%)	8 (11.9%)	71.6%
Alexander *et al*[58]	114	IHP	Melphalan TNF alone or both	1.5 mg/kg 1 mg	39.5 ℃-40 ℃	60 min	1	2 (1.8%)	67 (58.8%)	NR	NR	60.5%
van Iersel *et al*[59]	97	IHP	Melphalan	200 mg	39.5 ℃	60 min	1	3 (3.1%)	49 (50.5%)	23 (23.7%)	22 (22.7%)	53.6%
Rizell *et al*[60]	27	IHP	Melphalan With or without TNF	0.5, 1 and 2 mg/kg 30 μg	⩾ 40 ℃	40-60 min	1	2 (7.4%)	17 (63.0%)	2 (7.4%)	6 (22.2%)	69.4%
Pingpank *et al*[61]	27	PIHP	Melphalan	2-3.5 mg/kg	NR	60 min	2.64	2 (7.4%)	6 (22.2%)	NR	NR	29.6%
Alexander *et al*[62]	29	IHP	Melphalan	1.5 mg/kg	NR	60 min	1	3 (10%)	15 (52%)	NR	NR	62%

NR: Not reported. IHP: Isolated hepatic perfusion; PIHP: Percutaneous isolated hepatic perfusion.

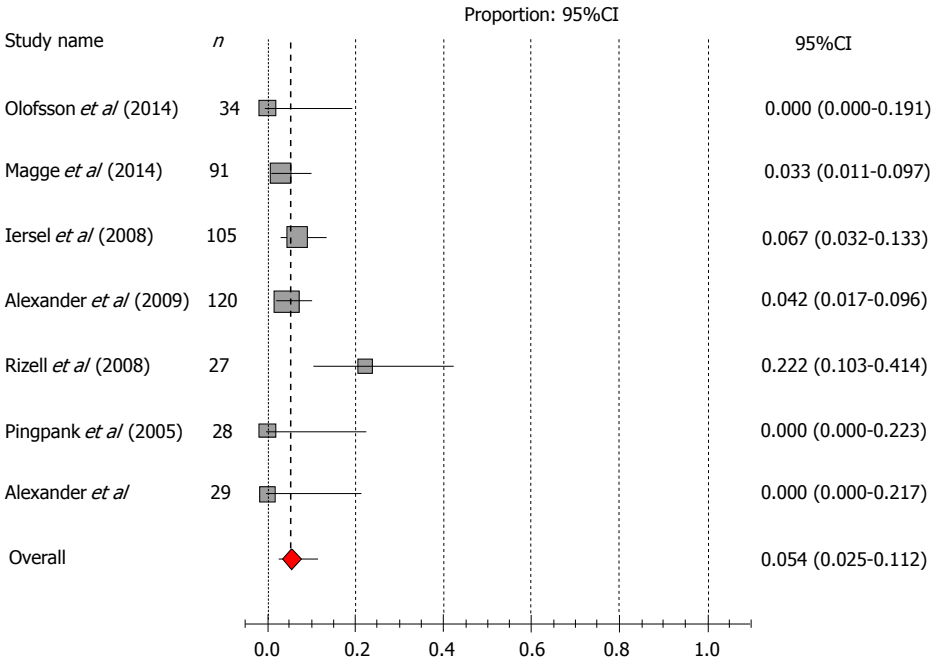

Figure 3 Forest plot of the studies for mortality. Pooled estimate (%) = 5.4%, 95%CI: 2.5%-11.2%, I^2 = 37.5%.

prolonged the duration of response from 5.8 to 13 mo (P < 0.001). Patients who received higher doses of Melphalan tended to have higher response rates (P = 0.034). In survival analysis, it was found that the use of hepatic artery infusion (HAI) following IHP (for OS: RR = 1.78, P = 0.0039, for PFS: RR = 2.79, P < 0.0001) and preoperative carcino-embryonic antigen (CEA) ≤ 30 ng/mL (for OS: RR = 2.29, P = 0.0012, for PFS: RR = 2.35, P = 0.0006) were independently associated with hepatic PFS and OS. A study carried out by van

Table 4 Isolated hepatic perfusion morbidity and mortality

Ref.	Mortality	Toxicity grade 3/4 (%)						Complications grade 3/4 (%)				
		Bilirubin	Transaminases	Alkaline phosphatase	Neutropenia	Platelets	Anemia	Hepatic artery obstruction	Hepatic failure	Bleeding	Hypotension	Wound infection
Olofsson *et al*[55]	None	NR	NR	NR	NR	NR	NR	2.90%	NR	NR	NR	NR
Magge *et al*[56]	3.30%	20.50%	50.00%	3.40%	2.30%	18.20%	50.00%	NR	5.70%	NR	0%	3.40%
Fukumoto *et al*[57]	NR	NR	77.90%	NR	44.10%	NR	NR	NR	NR	1.50%	NR	8.80%
Alexander *et al*[58]	4%	46.70%	55.80%	4.20%	0.80%	10.00%	NR	NR	3.30%	0.80%	5.80%	2.50%
van Iersel *et al*[59]	6%	18.00%	20.00%	15.20%	2.90%	NR	NR	1.90%	NR	8.60%	NR	NR
Rizell *et al*[60]	22%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pingpank *et al*[61]	None	18.9% (hepatic toxicity)			66.20%	35.10%	17.60%	NR	NR	NR	NR	NR
Alexander *et al*[62]	None	65.5% (hepatic toxicity)			NR	NR	NR	NR	NR	NR	NR	NR
Pooled P	5.4%				10.3	19.2	31.9%	2.2%	4.5%	4.50%	2.7%	5.7%
95%CI	(2.5%-11.2%)				(2%-39%)	(8.7%-37.2%)	(9.3%-68.1%)	(0.7%-6.6%)	(2.3%-8.4%)	(1.8-11.1%)	(0.3%-20.3%)	(3.1%-10.2%)

NR: Not reported.

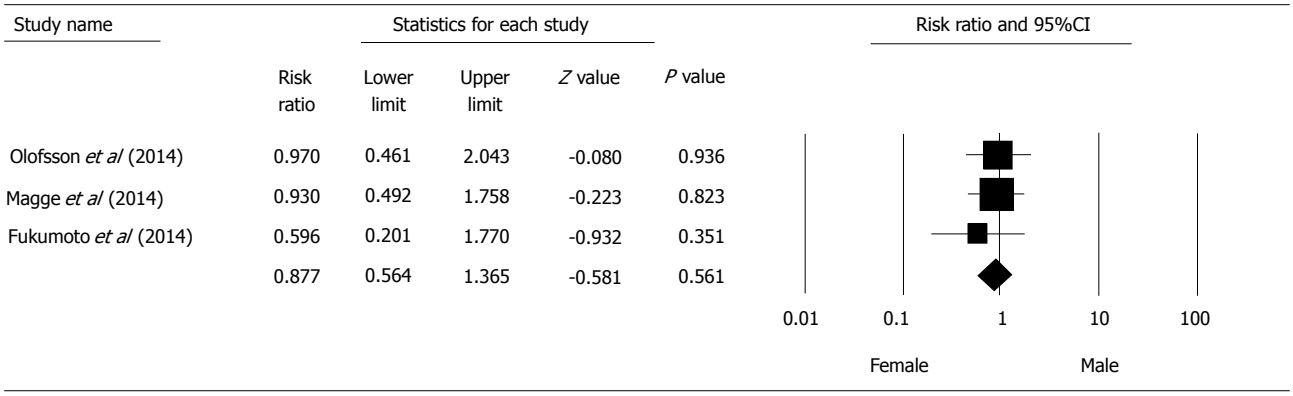

Figure 4 Forest plot of the relative risk of overall survival for different gender.

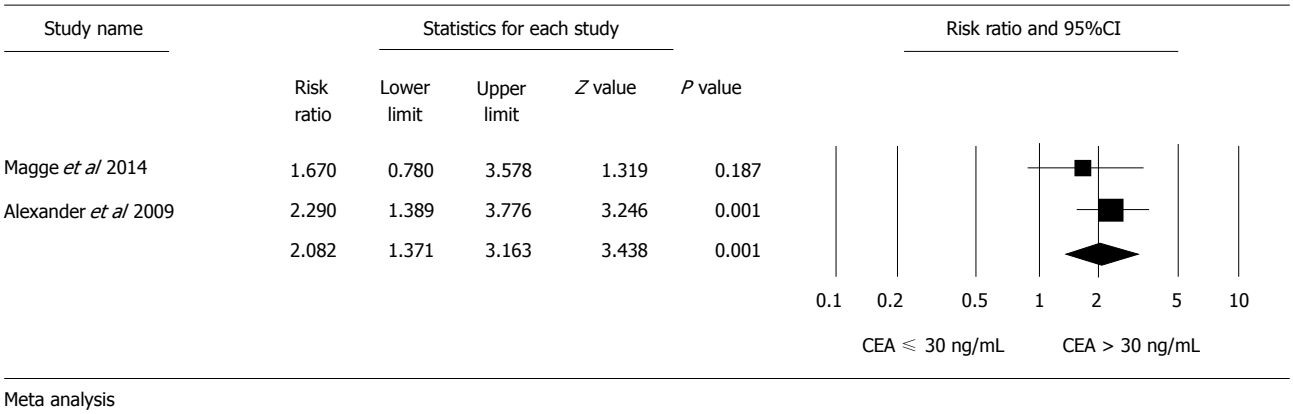

Figure 5 Forest plot of the relative risk of overall survival for different preoperative carcino-embryonic antigen levels. CEA: Carcino embryonic antigen.

Iersel *et al*[59] revealed that adjuvant chemotherapy was a positive prognostic factor for hepatic response to IHP (RR = 5.91, *P* = 0.009), while the female sex was borderline significant (RR = 2.65, *P* = 0.05). They confirmed adjuvant chemotherapy following IHP was a positive factor for PFS on multivariate analysis (RR = 0.05, *P* = 0.039), whereas on univariate analysis, no chemotherapy directed at liver metastases before IHP was a potential positive factor (*P* = 0.09). When assessed for OS, they found ⩾ 10 liver metastases (RR = 1.95, *P* = 0.006), absence of hepatic artery perfusion (RR = 4.15, *P* = 0.003), presence of postoperative complications (RR = 1.54, *P* = 0.048) were all negative factors. Alexander *et al*[58] reported that patients with Ocular Melanoma who have a baseline lactate dehydrogenase (LDH) > 160 U/L were likely to have shorter survival courses (RR = 17.1, *P* = 0.0062).

According to the prognostic factors mentioned above,

Table 5 Long-term survival outcomes after isolated hepatic perfusion

Ref.	Median follow-up (mo)	Median time to local progression (mo)	Median time to systemic progression (mo)	Median hepatic progression-free survival (mo)	Overall survival					
					Median OS (mo from IHP)	1-yr survival (%)	2-yr survival (%)	3-yr survival (%)	4-yr survival (%)	5-yr survival (%)
Olofsson *et al*[55]	NR	7 (0-31)	13 (2-34)	NR	24	NR	NR	NR	NR	NR
Magge *et al*[56]	NR	NR	NR	For CRC group: 12 (10.53-13.47) For CR: 12 For PR: 12 (10.1-13.9) For SD: 12.5 (10.53-13.47)	23 (15-28)	NR	NR	NR	NR	NR
Fukumoto *et al*[57]	20 (3-191)	NR	NR	NR	25	80.6%	NR	35.7%	NR	27.6%
Alexander *et al*[58]	78.1 (52.1-104.2)	7.3 (6.5-8.0)		NR	25 (19.4-30.6)	NR	53%	28%	14%	NR
van Iersel *et al*[59]	NR	NR	NR	7	17.4	NR	34%	NR	NR	NR
Rizell *et al*[60]	IHP I cohort: NR IHP II cohort: NR IHP III cohort: 7 (range 4-18)	NR	NR	NR	12.6 (2.5-57)	NR	NR	NR	NR	NR
Alexander *et al*[62] Median value (range)	11 (3-40)	8		12	12.1 (3-39+) 20 (12.1-25)	NR	NR	NR	NR	NR

OS: Overall survival; NR: Not reported; CRC: Colorectal cancer; CR: Complete response; PR: Partial response; SD: Stable disease.

Table 6 Summary of prognostic factors presented in relevant clinical trials

Ref.	Year	Prognostic factors for response	Prognostic factors for TTLP	Prognostic factors for PFS	Prognostic factors for OS
Olofsson *et al*[55]	2014	NR	Y	NR	Y
Magge *et al*[56]	2014	Y	NR	NR	Y
Fukumoto *et al*[57]	2014	NR	NR	NR	Y
Alexander *et al*[58]	2009	Y	NR	Y	Y
van Iersel *et al*[59]	2008	Y	NR	Y	Y
Rizell *et al*[60]	2008	NR	NR	NR	NR
Pingpank *et al*[61]	2005	NR	NR	NR	NR
Alexander *et al*[62]	2003	Y	NR	NR	Y

TTLP: Time to local progression; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

gender and preoperative CEA level predictive of survival were the only comparable factors with sufficient data for meta-analysis. Gender was not associated with overall survival (Figure 4); however, CEA $\leqslant$ 30 ng/mL was associated with a significant improvement in survival outcomes with CRC patients (RR = 2.082, 95%CI: 1.371-3.163) (Figure 5). There was no significant heterogeneity.

DISCUSSION

The ideal curative intervention of primary or secondary liver malignancies is surgical resection. Nonetheless, the diseases are unresectable in the majority of patients when diagnosed[2,63]. Systemic chemotherapy remains the first-line of palliative therapy for metastatic disease and, little benefit is gained from long-term prospective, although it is associated with good initial response rates. Better tumor response has been shown to correlate with significant systemic toxicity in the setting of high dosage of chemotherapy, which limits the application of systemic chemotherapy[64]. To circumvent such limitations, liver-directed regional therapies have emerged as novel therapeutic strategies. Regional therapies such as HAI, IHP, are based on the fact that higher doses of chemotherapy may improve the outcomes. HAI delivers chemotherapeutic regimens with a high rate of hepatic clearance directly to the hepatic artery, which provides the majority of blood supply to the tumor, thus avoiding systemic toxicity while achieving high concentrations of chemotherapeutic agents. The HAI method allows some regimens to achieve a 15-fold concentration in liver tumors compared to normal liver. IHP, which further blocks inferior vena cava (IVC), allows using more kinds of drugs and can reach up to 5 times higher tolerable drug doses than HAI without fear of systemic exposure[65]. That is, IHP allows broader regimens and gets higher concentrations, which would be lethal if administered systemically.

IHP has been investigating and reporting worldwide since its first description five decades ago[66]. Many studies evaluated the efficacy, safety, as well as the long-term survival of IHP, using generally accepted standards and yielded quantified results. Most studies acclaimed IHP to be efficacious and safe. Although promising, no current systemic evaluation of IHP is

available yet. Therefore we reviewed all the literature we could get and conducted a systemic review. As an alternate of IHP, here we discussed PIHP and IHP together.

Our systemic meta-analysis demonstrated a pooled response rate following IHP/PIHP treatment to be 60.8% (95%CI: 53.1%-68.0%), with each individual ranging from 29.6% to 71.6%. The median overall survival of IHP/PIHP was 20 mo (range: 12.1-25). This is particularly encouraging when considered with the low effects and high mortality with systemic chemotherapy. To our knowledge, there has been no randomized trial so far to compare the outcomes between IHP and systemic chemotherapy. A case-control study by van Iersel *et al*[53] for the first time revealed no statistical significance of overall survival (OS) between IHP and systemic chemotherapy in unresectable colorectal cancer liver metastases (median overall survival: 25.0 mo for IHP group and 21.7 mo for chemotherapy, $P = 0.29$). However, selection bias has to be considered given the disagreement of age and, the duration of follow-up between the two groups. Further investigations including randomized controlled trials are of great necessity to evaluate the efficacy of IHP/PIHP in comparison to conventional systemic chemotherapy and other regional therapies.

Most studies found the procedure of IHP and PIHP to be safe. Among the selected studies, mortality was varied between 0% and 6%, and we drew the pooled mortality rate to be 5.4%. Most investigators observed a transient liver toxicity, which manifested by increases of bilirubin and transaminases, and would approximately decrease to normal level by postoperative day 7. Grade 3-4 post-operative toxicity and major complications were listed in our review (Table 4). Albeit the major systemic toxicity was avoided and the mortality was acceptable, we still should take notice of selecting ideal patients to undergo these procedures.

Due to limited number and the heterogeneity of outcomes reported by different studies, the only definite prognostic factors with sufficient data for meta-analysis were gender and preoperative CEA levels predictive of survival (Figures 4 and 5). The result indicated that CRC patients with low preoperative CEA (≤ 30 ng/mL) tended to have a better outcome compared to those whose preoperative CEA level > 30 ng/mL. Of note, IHP followed by HAI has been reported as a positive factor of survival by several investigations[49,51,56,58]. However, due to the inconsistency or the absence of detailed parameters, we cannot get the results combined into an integrated one.

As a repeatable, less invasive method of hepatic perfusion *via* percutaneous administration, PIHP has been under clinical evaluation since the early 1990s[37,67]. Among all the studies, the majority was small-scale observational studies and case reports[21,24,36,68-70], and only two studies met our inclusion criteria. Fukumoto *et al*[57] performed 101 perfusions on 67 patients with hepatocellular carcinoma using Mitomycin C and/or Doxorubicin. They showed a hepatic response rate of 71.6% with overall survival of 25 mo, longer than the mean value of median OS of 19 mo reported by other six articles using IHP approach. Pingpank[71] described a response rate of 29.6% in phase Ⅰ study for patients with liver metastasis from various origins and of 34.1% in a phase Ⅲ trial for patients with liver metastasis from melanoma. The phase Ⅲ trial also reported the median hepatic PFS was longer in patients treated with PIHP than patients treated with standard of care (254 d *vs* 49 d). The distinction of response rates between these two sets of studies might be attributed to different cancer types and chemotherapy regimens. Additionally, in the phase Ⅰ study, the response rate was not good perhaps due to the fact that the study was designed to evaluate toxicity and subsequently determine the MTD during dose escalation. In other words, the response rate was not their primary end point. Meanwhile, in the phase Ⅲ study, the number of patients was relatively low, there were only a handful of patients who were refractory to systemic chemotherapy enrolled in the trial and associated with some withdrawers. All these factors might be selection bias for the study.

A number of limitations to this meta-analysis should not be ignored. All studies were non-randomized phase I/II clinical trials in design and may be liable to selection bias. Several aspects of heterogeneity may contribute to varied response and overall survival including pathological types of cancer, chemotherapy regimen, prior therapies, *etc*. In addition, the inconsistency of prognostic factors described in individual studies made it difficult to compare and evaluate in meta-analysis.

In general, IHP and PIHP have unique and obvious advantages compared to systemic chemotherapy. For decades, investigations of IHP and PIHP were continually conducted, different regimens, the combination of chemotherapy, hyperthermia and hypoxemia, variations for the inflow and the venovenous bypass have been tested to improve the efficacy and safety. The present systemic review and meta-analysis suggest that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary malignancies, exhibiting a relatively high response rate, low mortality rate, and potentially prolonged overall survival. Though the role of hepatic perfusion is still not fully understood, there are vacant areas need to be explored. Can IHP make benefits to patients who were chemorefractory? Will IHP followed by HAI play a more effective role than IHP does? Will it improve the outcomes when IHP is a component to therapy and is combined with systemic chemotherapy or other regional therapies? How effective is it when applied to other types of tumor, *e.g.*, pancreatic carcinoma? What kinds of patients would benefit most from this procedure? What is the appropriate timing of using IHP? And for percutaneous

perfusion, which of the alternative techniques would be better, and how many times should they be repeated in different patients? These questions remain to be solved. Continued evaluation and great efforts are required to clarify its role and greater benefit each patient.

COMMENTS

Background

The optimal curative treatment of primary or secondary liver tumors is surgical resection. However, less than one third of cases with malignant liver tumors are candidates for surgical intervention. Conventional chemotherapy may be applied systemically but little benefit is gained from long-term prospective. Better tumor response has been shown to correlate with significant systemic toxicity in the setting of high dosage of chemotherapy, which limits the application of systemic chemotherapy. Isolated hepatic perfusion (IHP) as a liver-directed regional therapy, completely separating the liver's blood supply from the rest of the body through a surgical operation, and allows extremely high tolerable drug doses without fear of systemic exposure. As an alternative approach of IHP, percutaneous IHP (PIHP) is performed *via* a minimally invasive approach, using a double-balloon catheter to cut the liver's circulation. Here the authors conduct this study to investigate the efficacy, safety and survival benefit of these approaches.

Research frontiers

IHP has been investigating since its first description five decades ago. As a repeatable, less invasive method of hepatic perfusion, PIHP has been under clinical evaluation since the early 1990s. For decades, investigations of IHP and PIHP were continually conducted, different regimens, the combination of chemotherapy, hyperthermia and hypoxemia, variations for the inflow and the venovenous bypass have been tested to improve the efficacy and safety. Most studies acclaimed that IHP and PIHP have unique and obvious advantages compared to systemic chemotherapy. The role of hepatic perfusion in multidisciplinary treatment approaches for unresectable liver malignancies is still not fully understood. Continued evaluation and great efforts are required to clarify its role and greater benefit each patient.

Innovations and breakthroughs

IHP and PIHP have been successfully performed to treat primary or secondary unresectable liver cancers in various studies. In the present systemic review the authors reviewed the literature, carefully extracted and investigated the data, demonstrated all details and results of this technique in every aspect, so that it will help readers to understand this technique in a quick, comprehensive and objective way.

Applications

This review suggests that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary malignancies, exhibiting a relatively high response rate, low mortality rate, and potentially prolonged overall survival.

Terminology

IHP is a surgical technique that completely separating the liver's circulation from the rest of the body's circulatory system. The isolation of the liver's circulation allows an extremely high concentration of chemotherapy to the whole organ, while minimizing systemic toxicity. The procedure requires an open surgery which can be done only once. As an alternative approach of IHP, PIHP is performed *via* a minimally invasive approach, using a double-balloon catheter to cut the liver's circulation under fluoroscopic guidance. PIHP obviate a large abdominal operation, and allows repeatable manipulation, which may enable the patients to get maximized therapeutic effects while having a faster recovery.

Peer-review

This is an interesting review regarding the IHP for unresectable hepatic malignancies. The review of this topic may be useful for readers.

REFERENCES

1 **Tzeng CW**, Aloia TA. Colorectal liver metastases. *J Gastrointest Surg* 2013; **17**: 195-201; quiz p.201-202 [PMID: 23054896 DOI: 10.1007/s11605-012-2022-3]

2 **Leporrier J**, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg* 2006; **93**: 465-474 [PMID: 16523446 DOI: 10.1002/bjs.5278]

3 **Reddy SK**, Kesmodel SB, Alexander HR. Isolated hepatic perfusion for patients with liver metastases. *Ther Adv Med Oncol* 2014; **6**: 180-194 [PMID: 25057304 DOI: 10.1177/1758834014529175]

4 **Facy O**, Doussot A, Zinzindohoué F, Holl S, Rat P, Ortega Deballon P. Isolated hepatic perfusion: principles and results. *J Visc Surg* 2014; **151** Suppl 1: S25-S32 [PMID: 24582276 DOI: 10.1016/j.jviscsurg.2013.12.006]

5 **Slim K**, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; **73**: 712-716 [PMID: 12956787]

6 **Wallace BC**, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol* 2009; **9**: 80 [PMID: 19961608 DOI: 10.1186/1471-2288-9-80]

7 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

8 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

9 **van Iersel LB**, de Leede EM, Vahrmeijer AL, Tijl FG, den Hartigh J, Kuppen PJ, Hartgrink HH, Gelderblom H, Nortier JW, Tollenaar RA, van de Velde CJ. Isolated hepatic perfusion with oxaliplatin combined with 100 mg melphalan in patients with metastases confined to the liver: A phase I study. *Eur J Surg Oncol* 2014; **40**: 1557-1563 [PMID: 25125340 DOI: 10.1016/j.ejso.2014.06.010]

10 **Tanaka M**, Fukumoto T, Kido M, Takebe A, Kuramitsu K, Kinoshita H, Komatsu S, Fukushima K, Urade T, So S, Shinzeki M, Matsumoto I, Ajiki T, Terashima K, Fujii O, Demizu Y, Fuwa N, Ku Y. Analysis of the safety and efficacy of percutaneous isolated hepatic perfusion after particle therapy for advanced hepatocellular carcinoma. *Gan To Kagaku Ryoho* 2013; **40**: 1681-1683 [PMID: 24393887]

11 **Magge D**, Zureikat AH, Bartlett DL, Holtzman MP, Choudry HA, Beumer JH, Pingpank JF, Holleran JL, Strychor S, Cunningham DE, Jones HL, Zeh HJ. A phase I trial of isolated hepatic perfusion (IHP) using 5-FU and oxaliplatin in patients with unresectable isolated liver metastases from colorectal cancer. *Ann Surg Oncol* 2013; **20**: 2180-2187 [PMID: 23575907 DOI: 10.1245/s10434-013-2960-3]

12 **Varghese S**, Xu H, Bartlett D, Hughes M, Pingpank JF, Beresnev T, Alexander HR. Isolated hepatic perfusion with high-dose melphalan results in immediate alterations in tumor gene expression in patients with metastatic ocular melanoma. *Ann Surg Oncol* 2010; **17**: 1870-1877 [PMID: 20221901 DOI: 10.1245/s10434-010-0998-z]

13 **Zeh HJ**, Brown CK, Holtzman MP, Egorin MJ, Holleran JL, Potter DM, Bartlett DL. A phase I study of hyperthermic isolated hepatic perfusion with oxaliplatin in the treatment of unresectable liver metastases from colorectal cancer. *Ann Surg Oncol* 2009; **16**: 385-394 [PMID: 19034580 DOI: 10.1245/s10434-008-0179-5]

14 **van Etten B**, de Wilt JH, Brunstein F, Eggermont AM, Verhoef C. Isolated hypoxic hepatic perfusion with melphalan in patients with irresectable ocular melanoma metastases. *Eur J Surg Oncol* 2009; **35**: 539-545 [PMID: 18760560 DOI: 10.1016/j.ejso.2008.07.004]

15 **Verzaro R**, Zeh H, Bartlett D. A safe and fast technique for isolated hepatic perfusion. *J Surg Oncol* 2008; **98**: 393-396 [PMID:

18646044 DOI: 10.1002/jso.21113]
16 **Verhoef C**, de Wilt JH, Brunstein F, Marinelli AW, van Etten B, Vermaas M, Guetens G, de Boeck G, de Bruijn EA, Eggermont AM. Isolated hypoxic hepatic perfusion with retrograde outflow in patients with irresectable liver metastases; a new simplified technique in isolated hepatic perfusion. *Ann Surg Oncol* 2008; **15**: 1367-1374 [PMID: 18239976 DOI: 10.1245/s10434-007-9714-z]
17 **Mocellin S**, Pilati P, Da Pian P, Forlin M, Corazzina S, Rossi CR, Innocente F, Ori C, Casara D, Ujka F, Nitti D, Lise M. Correlation between melphalan pharmacokinetics and hepatic toxicity following hyperthermic isolated liver perfusion for unresectable metastatic disease. *Ann Surg Oncol* 2007; **14**: 802-809 [PMID: 17103263 DOI: 10.1245/s10434-006-9108-7]
18 **van Etten B**, Brunstein F, van IJken MG, Marinelli AW, Verhoef C, van der Sijp JR, Guetens G, de Boeck G, de Bruijn EA, de Wilt JH, Eggermont AM. Isolated hypoxic hepatic perfusion with orthograde or retrograde flow in patients with irresectable liver metastases using percutaneous balloon catheter techniques: a phase I and II study. *Ann Surg Oncol* 2004; **11**: 598-605 [PMID: 15172933 DOI: 10.1245/ASO.2004.09.021]
19 **Noter SL**, Rothbarth J, Pijl ME, Keunen JE, Hartgrink HH, Tijl FG, Kuppen PJ, van de Velde CJ, Tollenaar RA. Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. *Melanoma Res* 2004; **14**: 67-72 [PMID: 15091197 DOI: 10.1097/00008390-200402000-00011]
20 **Lise M**, Pilati P, Da Pian P, Mocellin S, Ori C, Casara D, Rossi CR, Darisi T, Corazzina S, Nitti D. Hyperthermic isolated liver perfusion for unresectable liver cancers: pilot study. *J Chemother* 2004; **16** Suppl 5: 37-39 [PMID: 15675475]
21 **Ku Y**, Iwasaki T, Tominaga M, Fukumoto T, Takahashi T, Kido M, Ogata S, Takahashi M, Kuroda Y, Matsumoto S, Obara H. Reductive surgery plus percutaneous isolated hepatic perfusion for multiple advanced hepatocellular carcinoma. *Ann Surg* 2004; **239**: 53-60 [PMID: 14685100 DOI: 10.1097/01.sla.0000103133.03688.3d]
22 **Grover AC**, Libutti SK, Pingpank JF, Helsabeck C, Beresnev T, Alexander HR. Isolated hepatic perfusion for the treatment of patients with advanced liver metastases from pancreatic and gastrointestinal neuroendocrine neoplasms. *Surgery* 2004; **136**: 1176-1182 [PMID: 15657573 DOI: 10.1016/j.surg.2004.06.044]
23 **Feldman ED**, Wu PC, Beresneva T, Helsabeck C, Rodriguez M, Bartlett DL, Libutti SK, Pingpank JF, Alexander HR. Treatment of patients with unresectable primary hepatic malignancies using hyperthermic isolated hepatic perfusion. *J Gastrointest Surg* 2004; **8**: 200-207 [PMID: 15036196 DOI: 10.1016/j.gassur.2003.11.005]
24 **Savier E**, Azoulay D, Huguet E, Lokiec F, Gil-Delgado M, Bismuth H. Percutaneous isolated hepatic perfusion for chemotherapy: a phase 1 study. *Arch Surg* 2003; **138**: 325-332 [PMID: 12611582 DOI: 10.1001/archsurg.138.3.325]
25 **Alexander HR**, Libutti SK, Bartlett DL, Pingpank JF, Kranda K, Helsabeck C, Beresnev T. Hepatic vascular isolation and perfusion for patients with progressive unresectable liver metastases from colorectal carcinoma refractory to previous systemic and regional chemotherapy. *Cancer* 2002; **95**: 730-736 [PMID: 12209715 DOI: 10.1002/cncr.10686]
26 **Vahrmeijer AL**, van Dierendonck JH, Keizer HJ, Beijnen JH, Tollenaar RA, Pijl ME, Marinelli A, Kuppen PJ, van Bockel JH, Mulder GJ, van de Velde CJ. Increased local cytostatic drug exposure by isolated hepatic perfusion: a phase I clinical and pharmacologic evaluation of treatment with high dose melphalan in patients with colorectal cancer confined to the liver. *Br J Cancer* 2000; **82**: 1539-1546 [PMID: 10789721 DOI: 10.1054/bjoc.2000.1175]
27 **Takahashi T**, Ku Y, Tominaga M, Iwasaki T, Fukumoto T, Takamatsu M, Tsuchida S, Sendou H, Suzuki Y, Kuroda Y. Phase I study of super high-dose chemotherapy for liver cancer with percutaneous isolated hepatic perfusion (PIHP) and peripheral blood stem cell transplantation (PBSCT). *Gan To Kagaku Ryoho* 2000; **27**: 1801-1804 [PMID: 11086416]
28 **Alexander HR**, Libutti SK, Bartlett DL, Puhlmann M, Fraker DL, Bachenheimer LC. A phase I-II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2000; **6**: 3062-3070 [PMID: 10955785]
29 **Lindnér P**, Fjälling M, Hafström L, Kierulff-Nielsen H, Mattsson J, Scherstén T, Rizell M, Naredi P. Isolated hepatic perfusion with extracorporeal oxygenation using hyperthermia, tumour necrosis factor alpha and melphalan. *Eur J Surg Oncol* 1999; **25**: 179-185 [PMID: 10218462 DOI: 10.1053/ejso.1998.0623]
30 **Hwu WJ**, Salem RR, Pollak J, Rosenblatt M, D'Andrea E, Leffert JJ, Faraone S, Marsh JC, Pizzorno G. A clinical-pharmacological evaluation of percutaneous isolated hepatic infusion of doxorubicin in patients with unresectable liver tumors. *Oncol Res* 1999; **11**: 529-537 [PMID: 10905565]
31 **Oldhafer KJ**, Lang H, Frerker M, Moreno L, Chavan A, Flemming P, Nadalin S, Schmoll E, Pichlmayr R. First experience and technical aspects of isolated liver perfusion for extensive liver metastasis. *Surgery* 1998; **123**: 622-631 [PMID: 9626312 DOI: 10.1016/S0039-6060(98)70200-4]
32 **Oldhafer KJ**, Frerker MK, Lang H, Fauler J, Flemming P, Schmoll E, Nadalin S, Moreno L, Pichlmayr R. High-dose mitomycin C in isolated hyperthermic liver perfusion for unresectable liver metastases. *J Invest Surg* 1998; **11**: 393-400 [PMID: 9895113 DOI: 10.3109/08941939809032216]
33 **Nakajima Y**, Horikawa M, Kin T, Ohyama T, Kanehiro H, Hisanaga M, Nishio K, Nagao M, Sho M, Yamada T, Ohashi K, Ko S, Nakano H. Hyperthermo-chemo-hypoxic isolated liver perfusion for hepatic metastases: a possible adjuvant approach. *Recent Results Cancer Res* 1998; **147**: 28-41 [PMID: 9670266 DOI: 10.1007/978-3-642-80460-1_4]
34 **Hafström L**, Naredi P. Isolated hepatic perfusion with extracorporeal oxygenation using hyperthermia TNF alpha and melphalan: Swedish experience. *Recent Results Cancer Res* 1998; **147**: 120-126 [PMID: 9670274 DOI: 10.1007/978-3-642-80460-1_12]
35 **Marinelli A**, de Brauw LM, Beerman H, Keizer HJ, van Bockel JH, Tjaden UR, van de Velde CJ. Isolated liver perfusion with mitomycin C in the treatment of colorectal cancer metastases confined to the liver. *Jpn J Clin Oncol* 1996; **26**: 341-350 [PMID: 8895675 DOI: 10.1093/oxfordjournals.jjco.a023243]
36 **Ravikumar TS**, Pizzorno G, Bodden W, Marsh J, Strair R, Pollack J, Hendler R, Hanna J, D'Andrea E. Percutaneous hepatic vein isolation and high-dose hepatic arterial infusion chemotherapy for unresectable liver tumors. *J Clin Oncol* 1994; **12**: 2723-2736 [PMID: 7989950]
37 **Beheshti MV**, Denny DF, Glickman MG, Bodden W, Marsh JC, Strair R, Ravikumar TS. Percutaneous isolated liver perfusion for treatment of hepatic malignancy: preliminary report. *J Vasc Interv Radiol* 1992; **3**: 453-458 [PMID: 1515715 DOI: 10.1016/S1051-0443(92)71988-5]
38 **Lans TE**, Bartlett DL, Libutti SK, Gnant MF, Liewehr DJ, Venzon DJ, Turner EM, Alexander HR. Role of tumor necrosis factor on toxicity and cytokine production after isolated hepatic perfusion. *Clin Cancer Res* 2001; **7**: 784-790 [PMID: 11309322]
39 **Yamada T**, Hisanaga M, Nakajima Y, Kanehiro H, Aomatsu Y, Ko S, Kin T, Nishio K, Sho M, Nagao M, Harada A, Matsushima K, Nakano H. The serum interleukin 8 level reflects hepatic mitochondrial redox state in hyperthermochemohypoxic isolated liver perfusion with use of a venovenous bypass. *Surgery* 1999; **125**: 304-314 [PMID: 10076615 DOI: 10.1016/S0039-6060(99)70241-2]
40 **Wu PC**, McCart A, Hewitt SM, Turner E, Libutti SK, Bartlett DL, Alexander HR. Isolated organ perfusion does not result in systemic microembolization of tumor cells. *Ann Surg Oncol* 1999; **6**: 658-663 [PMID: 10560851 DOI: 10.1007/s10434-999-0658-3]
41 **Masucci IP**, Calis KA, Bartlett DL, Alexander HR, Horne MK. Thrombocytopenia after isolated limb or hepatic perfusions with melphalan: the risk of heparin-induced thrombocytopenia. *Ann Surg Oncol* 1999; **6**: 476-480 [PMID: 10458686 DOI: 10.1007/s10434-999-0476-7]
42 **De Vries MR**, Borel Rinkes IH, Swaak AJ, Hack CE, Van De Velde

CJ, Wiggers T, Tollenaar RA, Kuppen PJ, Eggermont AM. Acute-phase response patterns in isolated hepatic perfusion with tumour necrosis factor alpha (TNF-alpha) and melphalan in patients with colorectal liver metastases. *Eur J Clin Invest* 1999; **29**: 553-560 [PMID: 10354218 DOI: 10.1046/j.1365-2362.1999.00480.x]

43 **Alexander HR**, Brown CK, Bartlett DL, Libutti SK, Figg WD, Raje S, Turner E. Augmented capillary leak during isolated hepatic perfusion (IHP) occurs via tumor necrosis factor-independent mechanisms. *Clin Cancer Res* 1998; **4**: 2357-2362 [PMID: 9796965]

44 **Kuppen PJ**, Jonges LE, van de Velde CJ, Vahrmeijer AL, Tollenaar RA, Borel Rinkes IH, Eggermont AM. Liver and tumour tissue concentrations of TNF-alpha in cancer patients treated with TNF-alpha and melphalan by isolated liver perfusion. *Br J Cancer* 1997; **75**: 1497-1500 [PMID: 9166943 DOI: 10.1038/bjc.1997.255]

45 **He X**, Kong Y, Wen D, Liu C, Xiao M, Zhao G, Zhen Y, Zhang H. A prospective, randomized trial of pancreatectomy combined with isolated hepatic perfusion via a dual route or conventional postoperative adjuvant therapy in patients with advanced pancreatic head carcinoma. *Int J Clin Exp Med* 2015; **8**: 6463-6471 [PMID: 26131274]

46 **Awazu M**, Fukumoto T, Takebe A, Ajiki T, Matsumoto I, Kido M, Tanaka M, Kuramitsu K, Ku Y. Lymphadenectomy combined with locoregional treatment for multiple advanced hepatocellular carcinoma with lymph node metastases. *Kobe J Med Sci* 2013; **59**: E17-E27 [PMID: 23756659]

47 **Alexander HR**, Bartlett DL, Libutti SK, Fraker DL, Moser T, Rosenberg SA. Isolated hepatic perfusion with tumor necrosis factor and melphalan for unresectable cancers confined to the liver. *J Clin Oncol* 1998; **16**: 1479-1489 [PMID: 9552055]

48 **Libutti SK**, Barlett DL, Fraker DL, Alexander HR. Technique and results of hyperthermic isolated hepatic perfusion with tumor necrosis factor and melphalan for the treatment of unresectable hepatic malignancies. *J Am Coll Surg* 2000; **191**: 519-530 [PMID: 11085732 DOI: 10.1016/S1072-7515(00)00733-X]

49 **Bartlett DL**, Libutti SK, Figg WD, Fraker DL, Alexander HR. Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. *Surgery* 2001; **129**: 176-187 [PMID: 11174711 DOI: 10.1067/msy.2001.110365]

50 **Rothbarth J**, Pijl ME, Vahrmeijer AL, Hartgrink HH, Tijl FG, Kuppen PJ, Tollenaar RA, van de Velde CJ. Isolated hepatic perfusion with high-dose melphalan for the treatment of colorectal metastasis confined to the liver. *Br J Surg* 2003; **90**: 1391-1397 [PMID: 14598420 DOI: 10.1002/bjs.4308]

51 **Alexander HR**, Libutti SK, Pingpank JF, Bartlett DL, Helsabeck C, Beresneva T. Isolated hepatic perfusion for the treatment of patients with colorectal cancer liver metastases after irinotecan-based therapy. *Ann Surg Oncol* 2005; **12**: 138-144 [PMID: 15827794 DOI: 10.1245/ASO.2005.05.003]

52 **van Iersel LB**, Verlaan MR, Vahrmeijer AL, van Persijn van Meerten EL, Tijl FG, Sparidans RW, Gelderblom H, Kuppen PJ, Tollenaar RA, van de Velde CJ. Hepatic artery infusion of high-dose melphalan at reduced flow during isolated hepatic perfusion for the treatment of colorectal metastases confined to the liver: a clinical and pharmacologic evaluation. *Eur J Surg Oncol* 2007; **33**: 874-881 [PMID: 17400422 DOI: 10.1016/j.ejso.2007.02.022]

53 **van Iersel LB**, Koopman M, van de Velde CJ, Mol L, van Persijn van Meerten EL, Hartgrink HH, Kuppen PJ, Vahrmeijer AL, Nortier JW, Tollenaar RA, Punt C, Gelderblom H. Management of isolated nonresectable liver metastases in colorectal cancer patients: a case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy. *Ann Oncol* 2010; **21**: 1662-1667 [PMID: 20110289 DOI: 10.1093/annonc/mdp589]

54 **Schepers A**, Mieog S, van de Burg BB, van Schaik J, Liefers GJ, Marang-van de Mheen PJ. Impact of complications after surgery for colorectal liver metastasis on patient survival. *J Surg Res* 2010; **164**: e91-e97 [PMID: 20851414 DOI: 10.1016/j.jss.2010.07.022]

55 **Olofsson R**, Cahlin C, All-Ericsson C, Hashimi F, Mattsson J, Rizell M, Lindnér P. Isolated hepatic perfusion for ocular melanoma metastasis: registry data suggests a survival benefit. *Ann Surg Oncol* 2014; **21**: 466-472 [PMID: 24141377 DOI: 10.1245/s10434-013-3304-z]

56 **Magge D**, Choudry HA, Zeh HJ, Cunningham DE, Steel J, Holtzman MP, Jones HL, Pingpank JF, Bartlett DL, Zureikat AH. Outcome analysis of a decade-long experience of isolated hepatic perfusion for unresectable liver metastases at a single institution. *Ann Surg* 2014; **259**: 953-959 [PMID: 24169176 DOI: 10.1097/SLA.0000000000000261]

57 **Fukumoto T**, Tominaga M, Kido M, Takebe A, Tanaka M, Kuramitsu K, Matsumoto I, Ajiki T, Ku Y. Long-term outcomes and prognostic factors with reductive hepatectomy and sequential percutaneous isolated hepatic perfusion for multiple bilobar hepatocellular carcinoma. *Ann Surg Oncol* 2014; **21**: 971-978 [PMID: 24201744 DOI: 10.1245/s10434-013-3305-y]

58 **Alexander HR**, Bartlett DL, Libutti SK, Pingpank JF, Fraker DL, Royal R, Steinberg SM, Helsabeck CB, Beresneva TH. Analysis of factors associated with outcome in patients undergoing isolated hepatic perfusion for unresectable liver metastases from colorectal center. *Ann Surg Oncol* 2009; **16**: 1852-1859 [PMID: 19434456 DOI: 10.1245/s10434-009-0482-9]

59 **van Iersel LB**, Gelderblom H, Vahrmeijer AL, van Persijn van Meerten EL, Tijl FG, Putter H, Hartgrink HH, Kuppen PJ, Nortier JW, Tollenaar RA, van de Velde CJ. Isolated hepatic melphalan perfusion of colorectal liver metastases: outcome and prognostic factors in 154 patients. *Ann Oncol* 2008; **19**: 1127-1134 [PMID: 18304962 DOI: 10.1093/annonc/mdn032]

60 **Rizell M**, Mattson J, Cahlin C, Hafström L, Lindner P, Olausson M. Isolated hepatic perfusion for liver metastases of malignant melanoma. *Melanoma Res* 2008; **18**: 120-126 [PMID: 18337648 DOI: 10.1097/CMR.0b013e3282f8e3c9]

61 **Pingpank JF**, Libutti SK, Chang R, Wood BJ, Neeman Z, Kam AW, Figg WD, Zhai S, Beresneva T, Seidel GD, Alexander HR. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J Clin Oncol* 2005; **23**: 3465-3474 [PMID: 15908655 DOI: 10.1200/JCO.2005.00.927]

62 **Alexander HR**, Libutti SK, Pingpank JF, Steinberg SM, Bartlett DL, Helsabeck C, Beresneva T. Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2003; **9**: 6343-6349 [PMID: 14695133]

63 **Kim WR**, Gores GJ, Benson JT, Therneau TM, Melton LJ. Mortality and hospital utilization for hepatocellular carcinoma in the United States. *Gastroenterology* 2005; **129**: 486-493 [PMID: 16083705 DOI: 10.1016/j.gastro.2005.05.001]

64 **Surbone A**, DeVita VT. Dose intensity. The neglected variable in clinical trials. *Ann N Y Acad Sci* 1993; **698**: 279-288 [PMID: 8279768 DOI: 10.1111/j.1749-6632.1993.tb17219.x]

65 **de Brauw LM**, Marinelli A, van de Velde CJ, Hermans J, Tjaden UR, Erkelens C, de Bruijn EA. Pharmacological evaluation of experimental isolated liver perfusion and hepatic artery infusion with 5-fluorouracil. *Cancer Res* 1991; **51**: 1694-1700 [PMID: 1998960]

66 **Ausman RK**. Development of a technic for isolated perfusion of the liver. *N Y State J Med* 1961; **61**: 3993-3997 [PMID: 13863315]

67 **Curley SA**, Byrd DR, Newman RA, Carrasco CH, Cromeens D, Ellis HJ, Chase J, Dougherty T, Wright K, Bodden W. Hepatic arterial infusion chemotherapy with complete hepatic venous isolation and extracorporeal chemofiltration: a feasibility study of a novel system. *Anticancer Drugs* 1991; **2**: 175-183 [PMID: 1958862 DOI: 10.1097/00001813-199104000-00008]

68 **Urade T**, Tanaka M, Fukumoto T, Kido M, Tsuchida S, Takahashi M, Takebe A, Kuramitsu K, Awazu M, Chuma M, Fukushima K, So S, Tai K, Fujimoto M, Toyama H, Shinzeki M, Matsumoto I, Ajiki T, Ku Y. A case of bilobar multiple hepatocellular carcinoma in which complete remission was achieved by preoperative percutaneous isolated hepatic perfusion and subsequent hepatectomy. *Gan To Kagaku Ryoho* 2012; **39**: 1825-1827 [PMID: 23267899]

69 **Toyama H**, Matsumoto I, Shinzeki M, Shirakawa S, Tanaka M, Yamashita H, Ajiki T, Ueno K, Sawa H, Otsubo I, Murakami S, Kido M, Fukumoto T, Ku Y. A case of postoperative liver metastasis from pancreatic carcinoma treated with percutaneous

isolated hepatic perfusion(PIHP). *Gan To Kagaku Ryoho* 2012; **39**: 1886-1888 [PMID: 23267919]

70 **Maeda I**, Ku Y, Iwasaki T, Sugimoto T, Kusunoki N, Kuroda Y, Saitoh Y. A case of advanced cholangiocellular carcinoma treated successfully by percutaneous isolated liver perfusion with cisplatin. *Gan To Kagaku Ryoho* 1996; **23**: 1607-1609 [PMID: 8854818]

71 **Pingpank JF**. Melphalan for colorectal metastases to the liver. *Clin Adv Hematol Oncol* 2010; **8**: 175-177 [PMID: 20400932]

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META-ANALYSIS

Meta-analysis of lymph node metastasis in Siewert type Ⅰ and Ⅱ T1 adenocarcinomas

Hiroki Osumi, Junko Fujisaki, Masami Omae, Tomoki Shimizu, Toshiyuki Yoshio, Akiyoshi Ishiyama, Toshiaki Hirasawa, Tomohiro Tsuchida, Yorimasa Yamamoto, Hiroshi Kawachi, Noriko Yamamoto, Masahiro Igarashi

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Abstract

AIM

To evaluate the incidence of lymph node metastasis (LNM) and its risk factors in patients with Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas.

METHODS

We enrolled 85 patients [69 men, 16 women; median age (range), 67 (38-84) years] who had undergone esophagectomy or proximal gastrectomy for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Predictive risk factors of LNM included age, sex, location of the tumor center, confirmed Barrett's esophageal adenocarcinoma, tumor size, macroscopic tumor type, pathology, invasion depth, presence of ulceration, and lymphovascular invasion. Multivariate logistic regression analysis was used to identify factors predicting LNM. We also evaluated the frequencies of LNM for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas in meta-data analysis.

RESULTS

LNMs were found in 11 out of 85 patients (12.9%, 95%CI: 5.8-20.0). Only 1 of the 15 patients (6.6%, 95%CI: 0.0-19.2) who had a final diagnosis of pT1a adenocarcinoma had a positive LNM, whereas 10 of

the 70 patients (14.2%, 95%CI: 6.0-22.4) with a final diagnosis of pT1b adenocarcinoma had positive LNM. Furthermore, only one of the 30 patients (3.3%, 95%CI: 0.0-9.7) with a tumor invasion depth within 500 μm from muscularis mucosae had positive LNM. Poor differentiation and lymphovascular invasion were independently associated with a risk of LNM. In meta-data analysis, 12 of the 355 patients (3.3%, 95%CI: 1.5-5.2) who had a final diagnosis of pT1a adenocarcinoma had a positive LNM, whereas 91 of the 438 patients (20.7%, 95%CI: 16.9-24.5) with a final diagnosis of pT1b adenocarcinoma had positive LNM.

CONCLUSION

We consider endoscopic submucosal dissection (ESD) is suitable for patients with Siewert type Ⅰ and type Ⅱ T1a adenocarcinomas. For patients with T1b adenocarcinoma, especially invasion depth is within 500 μm from muscularis mucosae with no other risk factor for LNM, diagnostic ESD could be a treatment option according to the overall status of patients and the presence of comorbidities.

Key words: Siewert type Ⅰ and type Ⅱ adenocarcinomas; Lymph node metastasis

Core tip: We evaluated meta-analysis of the incidence of lymph node metastasis (LNM) in patients with Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Of previous 5 reports and our study, 12 of the 355 patients (3.38%, 95%CI: 1.5-5.2) in pT1a adenocarcinoma had LNM, whereas 91 of the 438 patients (20.7%, 95%CI: 16.9-24.5) in pT1b adenocarcinoma had LNM. We consider endoscopic submucosal dissection (ESD) to be a reasonable for patients that have well differentiated, limited to the mucosa, and within 30 mm in diameter with no lymphovascular invasion. For patients with T1b adenocarcinoma, especially invasion depth within 500 μm from muscularis mucosae with no other risk factor for LNM, diagnostic ESD could be a treatment option.

Osumi H, Fujisaki J, Omae M, Shimizu T, Yoshio T, Ishiyama A, Hirasawa T, Tsuchida T, Yamamoto Y, Kawachi H, Yamamoto N, Igarashi M. Meta-analysis of lymph node metastasis in Siewert type Ⅰ and Ⅱ T1 adenocarcinomas. *World J Meta-Anal* 2016; 4(6): 118-123 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i6/118.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i6.118

INTRODUCTION

Barrett's esophagus is most often diagnosed in people who have long term gastroesophageal reflux disease (GERD), which is a chronic regurgitation of acid from the stomach into the lower esophagus. It is associated with an increased risk of developing esophageal adenocarcinoma. The frequency of Barrett's esophageal adenocarcinoma (BEA) from Barrett's esophagus is about 0.5% per year[1]. However, the frequency of BEA is thought to be increasing because of the Westernization of dietary habits, obesity, and increased frequency of GERD associated with a decreasing frequency of *Helicobacter pylori* (*H. pylori*) infection in Japan.

Endoscopic submucosal dissection (ESD) for esophageal and gastric cancer is limited by the possible incidence of regional lymph node metastasis (LNM). There is robust data about the frequencies of LNM of squamous cell carcinoma or esophageal adenocarcinoma over the full length of esophagus. In contrast, there is a few data about the frequency of LNM for Siewert type Ⅰ and type Ⅱ pathological T1 (pT1) adenocarcinomas. Especially, there is only one report about the frequency of LNM for Siewert type Ⅱ pT1 adenocarcinomas from 2005 to 2015 in the PubMed database[2]. Siewert type Ⅰ was defined as adenocarcinoma of the distal esophagus, which usually arises from an area with Barrett's esophagus and may infiltrate the esophagogastric junction (EGJ) from above[3]. On the other hand, Siewert type Ⅱ was defined true carcinoma of the cardia arising immediately at the EGJ[3]. In this range, there are two types of adenocarcinomas: BEA from short or long segment Barret's esophagus develops from inflammation caused by exposure of the esophagus to gastric acid and bile; and gastric adenocarcinoma develops from mucosal atrophy and intestinal metaplasia, mainly caused by *H. pylori* infection[4].

If the frequency of LNM and the risk factors driving this process in this range can be determined, then patient treatment can be stratified: ESD can be offered to patients with tumors that have a low frequency of LNM; and surgical resection can be offered to patients with tumors that have a high frequency of LNM. The aim of this study was to evaluate the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas and its risk factors of LNM.

MATERIALS AND METHODS

Study population

There were 85 patients who received esophagectomy or proximal gastrectomy or additional surgery after ESD in Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas between January 2006 and December 2014 in our hospital. Our selection criteria were: (1) the center of the tumor was within 2 cm of the EGJ at the gastric side or within 5 cm of the EGJ at the oral side; (2) invasion depth was intramucosal or submucosal and was not reached the muscularis propria; and (3) patients had received primary surgery or additional surgery after ESD. Pathological evaluation was performed by two experienced pathologists (Kawachi H and Yamamoto N).

Tumor classifications

Differentiated pathology included papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated pathology included poorly differentiated adenocarcinoma, signet-

Table 1 Characteristics of patients with Siewert type I and II pT1 adenocarcinomas

Characteristic	Data
n	85
Median age (range), yr	67 (38-84)
Male sex, *n* (%)	69 (81.1)
Depth, *n* (%)	
T1a	22 (25.9)
T1b	63 (74.1)
Differentiation, *n* (%)	
Differentiated	72 (84.7)
Undifferentiated	13 (15.3)
Median size, (SD), mm	26 (± 14.6)
Lymphovascular invasion, *n* (%)	50 (58.8)
Underlying Barrett's esophagus, *n* (%)	43 (50.5)
Lymph node metastasis, *n* (%)	11 (12.9)

ring cell carcinoma, and mucinous adenocarcinoma. For the condition to be considered Barrett's esophagus, one of the following criteria must have been met: We could identify these pathologic findings in anal side of the tumor; esophageal glands, squamous island, and double layer of muscularis mucosae. Or we could find palisade vessels around the tumor endoscopically. Invasion depth was divided into T1a (Tumor confined to the mucosa) and T1b (Tumor confined to the submucosa) groups. T1b lesions were subclassified as: SM1 (tumor invasion is within 500 μm of the muscularis mucosae) or SM2 (tumor invasion is 500 μm or more deep into the muscularis mucosae). Assessment of the depth of tumor infiltration into the SM layer was based on the Japanese Classification of Gastric Carcinoma[5].

Meta-data analysis of the frequencies of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas

We searched for articles which were mentioned about the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas in the PubMed database from 2005 to 2015 using following terms: "T1," "esophagogastric junction adenocarcinoma", "esophageal adenocarcinoma", "lymph node metastasis", "early", "superficial". Terms were combined with "and/or" and asterisks. The main reasons of initial exclusion were as follows; squamous cell carcinoma was also included, esophageal adenocarcinoma of over the full length of esophagus, non-English literature, case reports, reviews and double publications.

This study was performed in accordance with the Declaration of Helsinki and approved by our Institutional Review Board (Registry number: 2015-1143).

Statistical analysis

Predictive risk factors included age, sex, location of tumor center (Siewert type Ⅰ or Ⅱ), presence of confirmed BEA (yes or no), tumor size (< 30 mm or ≥ 30 mm), macroscopic tumor type (elevated or depressed), pathology (undifferentiated or differentiated), depth of invasion (mucosal or SM, ≥ 500 μm or < 500 μm), presence of ulceration (yes or no), and presence of lymphovascular invasion (yes or no). All *P* values were the result of two-sided tests, and a *P* value of < 0.05 was considered statistically significant. Prognostic factors with a *P* value of < 0.2 in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing).

RESULTS

Clinical characteristics

Patient characteristics are shown in Table 1. This cohort included 85 patients (81.1% men and 18.9% women). The median age of patients at the time of surgery was 67 years (38-84). In total, 22 patients had pT1a tumors (25.9%) and 63 patients had pT1b tumors (74.1%). Median tumor size was 26 mm (± 14.6 mm). 72 patients (84.7%) had differentiated type tumor pathology and 13 patients (15.3%) had undifferentiated type tumor pathology. A total of 50 patients (58.8%) had lymphovascular invasion and 43 patients (50.5%) had underlying Barrett's esophagus.

Clinical outcomes and incidence of LNM

Overall, 11 out of 85 patients (12.9%, 95%CI: 5.8-20) had LNM. Table 2 shows the rate of LNM for each depth of invasion. There was a higher incidence of LNM in patients with pT1b compared with pT1a disease; however, this was not significant [14.2% (10/70) *vs* 6.6% (1/15), OR = 2.3, 95%CI: 0.28-108.3, *P* = 0.67]. Furthermore, for the actual depth of invasion, the frequencies of LNM were: < 500 μm, 3.3% (1/30, 95%CI: 0-9.7); < 1000 μm, 4.3% (2/46 95%CI: 0-10.2) (Table 3).

Univariate and multivariate logistic regression of risk factors of LNM

In the univariate analysis, poor differentiation (OR 6.6, 95%CI: 1.29-33.7, *P* = 0.01), and lymphovascular invasion (OR = 5.1, 95%CI: 1.04-25.1, *P* = 0.02) were risk factors for LNM; tumor size > 30 mm showed a tendency to be a risk factor (OR = 3.1, 95%CI: 0.72-14.8, *P* = 0.08). Multivariate logistic regression analysis identified poor tumor differentiation (OR = 6.08, 95%CI: 1.4-26.4, *P* = 0.01) and lymphovascular invasion (OR = 4.66, 95%CI: 1.09-19.9, *P* = 0.03) as independent predictors of a positive lymph node status (Table 4).

Meta-data analysis of the frequencies of LNM for Siewert types Ⅰ and Ⅱ pT1 adenocarcinomas

In total, we could find only 5 articles except for our study that were mentioned about the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas in the PubMed database from 2005 to 2015. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors. Furthermore, the frequencies of LNM

Table 2 Studies of patients who underwent surgery for Siewert type I and II pT1 adenocarcinomas with lymph node status

Ref.	*n*	Siewert classification	TNM classification		SM subdivision		
			T1a, *n* (%)	T1b, *n* (%)	SM1, *n* (%)	SM2, *n* (%)	SM3, *n* (%)
Westerterp *et al*[6]	120	Ⅰ, Ⅱ	1/54 (1.8)	18/66 (27.2)	0/25 (0)	6/23 (20)	12/18 (56)
Barbour *et al*[7]	85	Ⅰ, Ⅱ	0/35 (0)	9/50 (18)	-	-	-
Lees *et al*[8]	126	Ⅰ, Ⅱ	1/75 (1.3)	11/51 (21.6)	4/19 (21)	1/9 (11.1)	6/23 (26.1)
Griffin *et al*[9]	119	Ⅰ, Ⅱ	0/54 (0)	8/65 (12.3)	-	-	-
Lee *et al*[10]	258	Ⅰ, Ⅱ	9/122 (7.3)	35/136 (25.7)	-	-	-
Present study	85	Ⅰ, Ⅱ	1/15 (6.6)	10/70 (14.2)	0/7 (0)	4/43 (9.3)	6/20 (30)
Total	793	Ⅰ, Ⅱ	12/355 (3.4%, 95%CI: 1.5-5.2)	91/438 (20.7%, 95%CI: 16.9-24.5)			

TNM: Tumor-node-metastasis; SM: Submucosal; SM: Subdivision defines 3 sections of equivalent thickness of submucosa: Superficial (SM1), middle (SM2) and deep (SM3).

Table 3 Frequencies of lymph node metastasis and lymphovascular invasion per depth of invasion in this study

Invasion depth (μm)	Lymphatic invasion frequency	Venous invasion frequency	Frequency of lymph node metastasis
SM < 500, *n* (%, 95%CI)	7/30 (23.3, 8.1-38.4)	2/30 (6.6, 0-15.5)	1/30 (3.3, 0-9.7)
SM < 1000, *n* (%, 95%CI)	11/46 (23.9, 11.5-36.2)	7/46 (15.2, 4.5-25.5)	2/46 (4.3, 0-10.2)

SM: Submucosal.

Table 4 Univariate and multivariate analysis of potential risk factors for lymph node metastasis

Statistical test	OR	Lower 95%CI	Upper 95%CI	*P* value
Univariate analysis				
Age (< 70 or ≥ 70 yr)	0.32	0.03	1.75	0.19
Sex (male or female)	1.04	0.18	11	1
Location of tumor center (Siewert type Ⅰ or Ⅱ)	2.1	0.31	10.8	0.37
Depth of invasion (M or SM)	2.3	0.28	108.3	0.67
Depth of invasion (≥ 500 μm or < 500 μm)	4.89	0.58	40.8	0.14
Differentiation (undifferentiated or differentiated)	6.6	1.29	33.7	0.01
Tumor size (< 30 mm or ≥ 30 mm)	3.1	0.72	14.8	0.08
Macroscopic tumor type (elevated or depressed)	1.43	0.31	9.1	0.74
Ulceration (yes or no)	1.91	0.44	8.7	0.33
Barrett's esophageal adenocarcinoma (yes or no)	0.79	0.17	3.42	0.75
Lymphovascular invasion (yes or no)	5.1	1.04	25.1	0.02
Multivariate analysis				
Differentiation (undifferentiated or differentiated)	6.08	1.4	26.4	0.01
Lymphovascular invasion (yes or no)	4.66	1.09	19.9	0.03

M: Mucosal; SM: Submucosal; OR: Odds ratio.

were 9.1% (4/44, 95%CI: 0.5-17.5) for SM1, 22.5% (7/31, 95%CI: 7.8-37.2) for SM2, and 43.9% (18/41, 95%CI: 27-59) for SM3 (Table 2).

DISCUSSION

Our date showed that the frequency of LNM was 14.2% (10/70, 95%CI: 6-22.4) for pT1b and 6.6% (1/15, 95%CI: 0-19.2) for pT1a disease. The frequencies of LNM were 3.3% (1/30, 95%CI: 0-9.7) and 4.3% (2/46, 95%CI: 0-10.2) for invasion depths of < 500 μm and < 1000 μm, respectively. Logistic regression multivariate analysis identified poor differentiation and lymphovascular invasion as independent risk factors of LNM. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors in meta-analysis.

As I mentioned before, fewer data of LNM are available for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Especially, we could find only one report which mentioned the frequency of LNM for Siewert type Ⅱ pT1 adenocarcinoma using pubmed data base from 2005 to 2015[2]. The study included 453 patients: The incidence of LNM was 9.5% (16/173, 95%CI: 4.9-13.5) for pT1a tumors and 22.9% (61/280, 95%CI: 16.6-28.1) for pT1b tumors. Infiltration of the submucosa, tumor size of over 10 mm, and poor tumor differentiation were independently associated with a risk of LNM. On the other hand, when the search was restricted to patients with Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas (as in the present study), there were five reports that reviewed the frequency of LNM[6-10]. Table 2 and 3 shows summary data

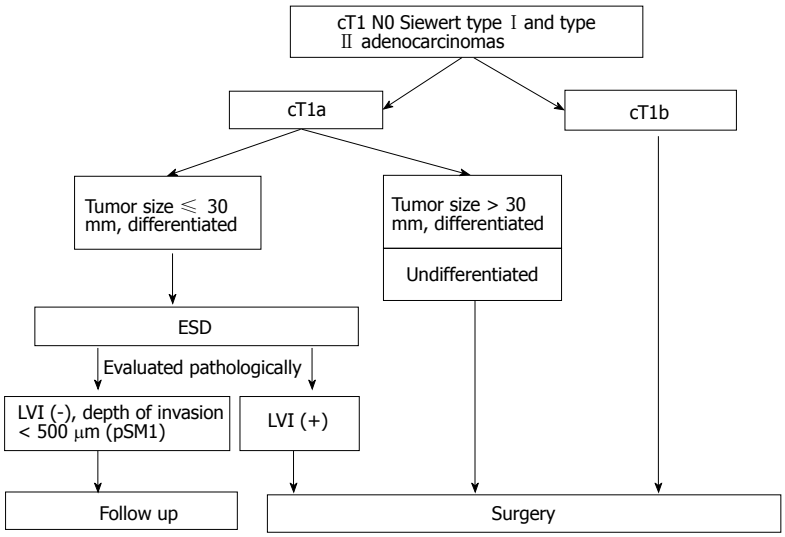

Figure 1 Our strategy of endoscopic submucosal dissection for T1 Siewert type Ⅰ and type Ⅱ adenocarcinomas. ESD: Endoscopic submucosal dissection.

from those studies. There was an increase in the rate of LNM with increasing SM category. In a study of the risk factors for LNM, Lees *et al*[10] described the features of LNM of a pT1a adenocarcinoma with lymphovascular invasion: a tumor size of 22 mm and poor differentiation. Barbour *et al*[7] recommended that patients with lymphovascular invasion or poorly differentiated adenocarcinomas should undergo adjuvant chemotherapy after surgery.

Thus far we described published data on each site of adenocarcinomas and then evaluated the frequency of LNM for each invasion depth category for both BEA and gastric adenocarcinoma. Dunbar and Spechler reported the frequency of LNM in Barrett's esophagus patients with high grade dysplasia (HGD) and pT1a adenocarcinoma in a systematic review[11]. In a total of 70 relevant reports, there were 1874 Barrett's esophagus patients who had undergone esophagectomy for HGD or pT1a adenocarcinoma. LNM were found in 26 patients (1.4%, 95%CI: 0.9-1.9). There were no metastases in the 524 patients with a final pathology diagnosis of HGD; in contrast, 26 (1.9%, 95%CI: 1.2-2.7) of the 1350 patients with a final diagnosis of pT1a adenocarcinoma had LNM. Gotoda *et al*[12] reported the frequency of LNM of pT1a gastric cancer. Of the 3016 pT1a cancers; only 65 (2.2%, 95%CI: 1.6-2.6) patients were associated with regional LNM. Depressed or ulcerated lesions of over 30 mm diameter, undifferentiated histology and invasion into lymph nodes or venules were associated with an increased risk of LNM. Therefore, the risk of unexpected LNM in both intramucosal BEA and gastric adenocarcinoma patients is in the range of 1%-2%.

On the other hand, Gockel *et al*[13] reported the risk of LNM in pT1b esophageal adenocarcinoma patients in a systematic review. The pooled outcomes for 7645 patients with esophageal adenocarcinoma involving tumor infiltration to the submucosal level were analyzed. Esophageal adenocarcinoma patients with SM1 lesions had the lowest incidence of LNM, and there was an increasing rate of LNM with increasing depth of SM invasion: 6% (4/65, 95%CI: 0.3-11.9) for SM1, 23% (10/44, 95%CI: 10.3-35.1) for SM2, and 58% (33/57, 95%CI: 45-70.7) for SM3. In gastric pT1b adenocarcinoma, Gotoda *et al*[12] also reported that 2249 tumors had penetrated the SM and 402 tumors invading the SM (17.9%, 95%CI: 16.2-19.4) were associated with LNM. There was a significant correlation of both tumor size over 30 mm and lymphovascular involvement with an increased risk of LNM. In addition, cancers that penetrated deep into the SM were the most likely to be associated with regional LNM.

Based on these results, we currently consider ESD to be a reasonable treatment for Siewert types Ⅰ and Ⅱ T1a adenocarcinomas that is well differentiated, limited to the mucosa, and within 30 mm in diameter with no lymphovascular invasion (Figure 1). In this study, although only one patient with LNM had pT1a adenocarcinoma, this patient had other risk factors for LNM (tumor size was 82 mm. Pathology was mixed type of tubular adenocarcinoma and signet cell adenocarcinoma. Vascular invasion was positive). On the other hand, the frequency of LNM was high in previous report on pT1b tumors, therefore we think T1b tumors are not appropriate for ESD. Indeed, However, the frequency of LNM was relatively low for tumors of within 500 μm from muscularis mucosae in this study (3.3%; 1/30, 95%CI: 0-9.7). Gotoda *et al*[12] reported that 145 patients with a tumor size of under 30 mm, differentiated histology, no lymphovascular invasion, and submucosal penetration of under 500 μm were entirely free of nodal metastasis (95%CI: 0-2.5%). Furthermore, although the 5-year survival rate for pT1b gastric cancer patients (except for death caused other disease) was 96.7%[14], and esophagectomy has a mortality rate that is 2%-11% higher than that of gastrectomy[3,15,16]. Therefore, diagnostic ESD could be a treatment option for patients with T1b tumors, especially those within 500 μm from muscularis mucosae without other risk factors of LNM, according to the patient's overall status and the presence of comorbidities (Figure 1). Even so, it is difficult to diagnose invasion depth correctly before ESD in this range. More patients undergoing surgery should be

persuaded to accept ESD.

COMMENTS

Background

Barrett's esophagus is most often diagnosed in people who have long term gastroesophageal reflux disease (GERD), which is a chronic regurgitation of acid from the stomach into the lower esophagus. It is associated with an increased risk of developing esophageal adenocarcinoma. The frequency of Barrett's esophageal adenocarcinoma (BEA) from Barrett's esophagus is about 0.5% per year. However, the frequency of BEA is thought to be increasing because of the Westernization of dietary habits, obesity, and increased frequency of GERD associated with a decreasing frequency of *Helicobacter pylori* (*H. pylori*) infection in Japan.

Research frontiers

If the frequency of lymph node metastasis (LNM) and the risk factors driving this process in this range can be determined, then patient treatment can be stratified: ESD can be offered to patients with tumors that have a low frequency of LNM; and surgical resection can be offered to patients with tumors that have a high frequency of LNM.

Innovations and breakthroughs

These date showed that the frequency of LNM was 14.2% (10/70, 95%CI: 6-22.4) for pT1b and 6.6% (1/15, 95%CI: 0-19.2) for pT1a disease. The frequencies of LNM were 3.3% (1/30, 95%CI: 0-9.7) and 4.3% (2/46, 95%CI: 0-10.2) for invasion depths of < 500 μm and < 1000 μm, respectively. Logistic regression multivariate analysis identified poor differentiation and lymphovascular invasion as independent risk factors of LNM. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors in meta-analysis.

Applications

The authors evaluated the frequencies of LNM for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas in meta-data analysis.

Peer-review

This paper has shown accurate incidence of lymph nodes metastasis of esophageal adenocarcinomas. Their study provides us important information related to treatment of esophageal adenocarcinomas.

REFERENCES

1 **Curvers WL**, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, Bohmer C, Mallant-Hent RC, van Oijen A, Naber AH, Scholten P, Busch OR, Blaauwgeers HG, Meijer GA, Bergman JJ. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol* 2010; **105**: 1523-1530 [PMID: 20461069 DOI: 10.1038/ajg.2010.171]

2 **Dubecz A**, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of Lymph Node Metastasis in Surgically Resected T1 Esophageal Cancer. *Ann Thorac Surg* 2015; **99**: 1879-1885; discussion 1886 [PMID: 25929888]

3 **Rüdiger Siewert J**, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000; **232**: 353-361 [PMID: 10973385 DOI: 10.1097/00000658-200009000-00007]

4 **Horii T**, Koike T, Abe Y, Kikuchi R, Unakami H, Iijima K, Imatani A, Ohara S, Shimosegawa T. Two distinct types of cancer of different origin may be mixed in gastroesophageal junction adenocarcinomas in Japan: evidence from direct evaluation of gastric acid secretion. *Scand J Gastroenterol* 2011; **46**: 710-719 [PMID: 21446884 DOI: 10.3109/00365521.2011.565069]

5 **Japanese Gastric Cancer Association.** Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

6 **Westerterp M**, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJ, Bergman JJ, Siersema PD, van Dekken H, van Lanschot JJ. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch* 2005; **446**: 497-504 [PMID: 15838647 DOI: 10.1007/s00428-005-1243-1]

7 **Barbour AP**, Jones M, Brown I, Gotley DC, Martin I, Thomas J, Clouston A, Smithers BM. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. *Ann Surg Oncol* 2010; **17**: 2494-2502 [PMID: 20349213 DOI: 10.1245/s10434-010-1025-0]

8 **Leers JM**, DeMeester SR, Oezcelik A, Klipfel N, Ayazi S, Abate E, Zehetner J, Lipham JC, Chan L, Hagen JA, DeMeester TR. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. *Ann Surg* 2011; **253**: 271-278 [PMID: 21119508 DOI: 10.1097/SLA.0b013e3181fbad42]

9 **Griffin SM**, Burt AD, Jennings NA. Lymph node metastasis in early esophageal adenocarcinoma. *Ann Surg* 2011; **254**: 731-776; discussion 731-776 [PMID: 21997815 DOI: 10.1097/SLA.0b013e318236048b]

10 **Lee L**, Ronellenfitsch U, Hofstetter WL, Darling G, Gaiser T, Lippert C, Gilbert S, Seely AJ, Mulder DS, Ferri LE. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. *J Am Coll Surg* 2013; **217**: 191-199 [PMID: 23659947 DOI: 10.1016/j.jamcollsurg.2013.03.015]

11 **Dunbar KB**, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2012; **107**: 850-862; quiz 863 [PMID: 22488081 DOI: 10.1038/ajg.2012.78]

12 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]

13 **Gockel I**, Sgourakis G, Lyros O, Polotzek U, Schimanski CC, Lang H, Hoppo T, Jobe BA. Risk of lymph node metastasis in submucosal esophageal cancer: a review of surgically resected patients. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 371-384 [PMID: 21651355 DOI: 10.1586/egh.11.33]

14 **Sasako M**, Kinoshita T, Maruyama K. The prognosis of early gastric cancer. *Stomach Intest* 1983; **28**: 139-146

15 **Yamashita H**, Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. *Ann Surg* 2011; **254**: 274-280 [PMID: 21772128 DOI: 10.1097/SLA.0b013e3182263911]

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