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Peer Reviewer of *World Journal of Clinical Oncology*, Jorge Gutiérrez-Cuevas, PhD, Professor, Department of Molecular Biology and Genomics, Institute for Molecular Biology in Medicine and Gene Therapy, CUCS, University of Guadalajara, Guadalajara 44340, Jalisco, Mexico. gutierrezcj05@gmail.com

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REVIEW

Stromal inflammation, fibrosis and cancer: An old intuition with promising potential

Oliver Oey, Angela Felicia Sunjaya, Yasir Khan, Andrew Redfern

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Oliver Oey, Faculty of Medicine, University of Western Australia, Perth 6009, Crawley NA, Australia

Oliver Oey, Department of Medical Oncology, Sir Charles Gardner Hospital, Nedlands 6009, Australia

Angela Felicia Sunjaya, Institute of Cardiovascular Science, University College London, London WC1E 6DD, United Kingdom

Yasir Khan, Department of Medical Oncology, St John of God Midland Public and Private Hospital, Midland 6056, WA, Australia

Andrew Redfern, Department of Medical Oncology, Fiona Stanley Hospital, Murdoch 6150, WA, Australia

Corresponding author: Angela Felicia Sunjaya, BMed, MD, Master's Student, Researcher, Institute of Cardiovascular Science, University College London, 62 Huntley St, London WC1E 6DD, United Kingdom. angelafelicia.s@gmail.com

Abstract

It is now well established that the biology of cancer is influenced by not only malignant cells but also other components of the tumour microenvironment. Chronic inflammation and fibrosis have long been postulated to be involved in carcinogenesis. Chronic inflammation can promote tumorigenesis *via* growth factor/cytokine-mediated cellular proliferation, apoptotic resistance, immunosuppression; and free-radical-induced oxidative deoxyribonucleic acid damage. Fibrosis could cause a perturbation in the dynamics of the tumour microenvironment, potentially damaging the genome surveillance machinery of normal epithelial cells. In this review, we will provide an in-depth discussion of various diseases characterised by inflammation and fibrosis that have been associated with an increased risk of malignancy. In particular, we will present a comprehensive overview of the impact of alterations in stromal composition on tumorigenesis, induced as a consequence of inflammation and/or fibrosis. Strategies including the application of various therapeutic agents with stromal manipulation potential and targeted cancer screening for certain inflammatory diseases which can reduce the risk of cancer will also be discussed.

Key Words: Inflammation; Fibrosis; Tumour microenvironment; Stroma; Cancer

Core Tip: Chronic inflammation and fibrosis have long been postulated to be involved in carcinogenesis *via* numerous mechanisms including but not limited to growth factor/cytokine-mediated cellular proliferation, apoptotic resistance, immunosuppression; and free-radical-induced oxidative deoxyribonucleic acid damage. In this review, we discuss various inflammatory and/or fibrotic conditions that have been associated with increased cancer risk, with particular emphasis on their pathophysiology. We also review various therapeutic agents and specific cancer screening that could be applicable in reducing the incidence of cancers developing from the corresponding inflammatory and/or fibrotic conditions, thereby reducing morbidity and mortality.

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INTRODUCTION

In recent years, there is growing consensus that the biology of cancer is not solely defined by malignant cells, but also by the surrounding tumour microenvironment (TME). The TME consists of cellular and non-cellular stroma. The concept that the TME may influence cancer biology was inspired by the observation of immune cells surrounding the tumour by Rudolf Virchow in 1863, and "the seed and soil theory" by Stephen Paget in 1889, in which he hypothesised that the metastatic destination of a certain cancer is dependent on similarities between the TME of primary tumour and the microenvironment at the site of metastases[1,2]. Since then, there have been significant advancements in the understanding of the impact of the TME on the behaviour of malignant cells, from initial tumorigenesis, through progression to therapy resistance[3-5]. This review will focus on the impact of both the physiological and pathological tissue microenvironment, particularly stromal fibrosis and inflammation, on tumorigenesis.

In this context, stroma refers to the component of an organ which provides biomechanical and nutritional support to the corresponding parenchyma. Specifically, it comprises of immune cells, fibroblasts, mesenchymal stromal cells, endothelial cells, pericytes, adipocytes, and the extracellular matrix (ECM). The ECM, consisting of collagen, proteoglycans, glycosaminoglycans and other macromolecules, provides structural and biochemical support for cellular components in the surrounding parenchyma. Of note, some authors do not include immune cells as a component of stroma, however, immune cells such as macrophages, neutrophils and lymphocytes, play an integral role to the function of parenchymal cells and can have far-reaching effects on tumour biology and consequent behaviour, as such they will be classified as a stromal component in this review.

Many stromal components have been shown through various in vitro and animal studies to influence the behaviour and fate of normal cells, including altering the risk of malignant transformation[6-8]. Inflammation and fibrosis are both common processes that significantly alter the cellular and ECM components of normal stroma and so may influence or underlie such behavioural shifts. Both processes have been seen to upregulate the expression of several tumorigenic signalling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducers and activators of transcription (STAT), wingless-related integration site (Wnt) and phosphatidylinositide 3-kinase (PI3K) *via* the release of pro inflammatory cytokines[9-12]. Hence, several inflammatory and fibrotic conditions have been linked as triggers for tumour development in the organ involved, whether due to autoimmune responses (inflammatory bowel disease and colorectal cancer[13]), bacterial or viral infections (pneumonia or tuberculosis with lung cancer[14]) and environmental factors (silica and lung cancer[15]).

Often, these pathological processes appear to be required for tumorigenesis rather than simply an overrepresentation of certain otherwise normal stromal components. For instance, inflamed adipose mammary tissue in the context of obese mice, increases myofibroblasts number, promoting fibrosis and transformation of normal to malignant breast tissue[6], whereas normal mouse fibroblasts have been shown to prevent clonal proliferation of polyoma virus-transformed cells *in vitro*[7]. However, there are less frequent precedents where normal stromal components may also contribute to tumorigenesis. Normal fibroblasts have been demonstrated to promote the generation of breast cancer stem cells[8]. Additionally, high mammographic breast density, which results from a higher density of stromal and glandular breast components and a lower proportion of adipocytes, is a potent risk factor for breast cancer development.

In this review we will discuss various medical conditions substantively characterised by inflammation and fibrosis, specifically those known to be linked to increased cancer risk. Furthermore, we will look to whether scenarios exist where physiological variations in stromal composition correlate with differing cancer incidence. In doing so, we will discuss the biological contribution of the various stromal components to tumorigenesis known to date and discuss interventions that may influence these processes to achieve therapeutic advantage.

PATHOLOGICAL INFLAMMATION, FIBROSIS AND CANCER RISK

A range of medical conditions exist that involve one or both of these processes. A common evolution pathogenically is of initial inflammation with subsequent fibrosis. However, each of the processes may occur in isolation. Here we look across a range of scenarios at whether each may affect cancer risk in isolation or whether both appear to be required for tumorigenesis (Table 1).

INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER

Inflammatory bowel disease (IBD) is sub-divided into ulcerative colitis (UC), which affects only the large bowel, and Crohn's disease (CD) which can involve any area of the gut from mouth to rectum[16]. The risk of developing colorectal cancer in UC patients is elevated compared to the disease-free population, with an overall risk of 4.8[13]. Similarly, in CD risk is elevated although to a more moderate degree, by 2-3 times[17]. In keeping with the small bowel involvement in CD, small intestinal tumours are also increased, by a relative risk of 18.75%[17]. The risk in both conditions is associated with duration and extent of inflammation[18]. Beyond inflammation, both conditions can also result in fibrosis although the pattern differs. Fibrosis leading to eventual stricture and potential obstruction is more common in CD than UC, with around 25% of CD sufferers eventually destined to develop a stricture over the course of the illness[19]. On initial consideration this appears at odds with the risk of colorectal cancer, but may be explained by the distribution of fibrotic change. In UC fibrosis is often superficial, affecting only the mucosal and sub-mucosal layers[20] but still, therefore, able to impact the epithelial layer from which neoplasms arise, and generally impacting a longer continuous length of colon. In contrast, Crohn's disease is characterized by patchy change and skip lesions such that the total area of involved epithelium is often less[16].

Considering these patterns and parallel links in other organs between inflammation, fibrosis and neoplastic transformation, the development of colitis-associated carcinoma (CAC) appears highly likely to be directly attributable to chronic inflammation and consequent fibrosis[21,22]. There is a biological rationale, with previous studies showing that certain inflammatory cytokines prominent in UC, namely TNF-α, IL-6 and TGF-β can promote a pro-tumorigenic microenvironment by stimulating essential cancer stem cell pathways, evading growth suppressors, and resisting apoptosis[23-25]. This occurs *via* induction of various molecular signalling pathways including NF-κB[9], STAT[26] and Wnt pathways[27]. Incidentally, these cytokines can also promote fibrosis. TNF-α has been demonstrated to induce IL-6 production, which is partly responsible for proliferation of fibroblasts[28,29]. In addition, TGF-β, highly expressed in intestinal epithelial cells, inflammatory cells and fibroblasts is known to induce fibrogenesis and ultimately the deposition of ECM such as collagen, *via* the Wnt/β-catenin pathway, which is also often activated early in dysplastic and surrounding non-dysplastic intestinal epithelial cells, in the setting of CAC carcinogenesis[10,30,31]. This concurs with the upregulation of type 1 collagen, revealed by proteomic analysis in the early stages of colorectal carcinogenesis[32]. Whether or not collagen promotes CAC carcinogenesis remains ambiguous, however increase in collagen may disrupt the polarity of healthy intestinal epithelial cells and stimulate cellular proliferation, thereby promoting malignant transformation.

While it is generally understood that fibrosis occurs as a result of chronic inflammation, it is now understood that fibrosis in IBD may occur without inflammation[33], and further that not all people with IBD develop fibrosis[34]. This prompts the question as to whether either fibrosis or inflammation without the companion process can also trigger carcinogenesis – a question which remains unanswered today due to a lack of cohorts with data that allow the linking degrees of inflammation and fibrosis to cancer risk.

CHRONIC PANCREATITIS AND PANCREATIC DUCTAL ADENOCARCINOMA

Chronic pancreatitis (CP) is a major risk factor for the development of pancreatic ductal adenocarcinoma (PDAC), increasing the risk of PDAC by 20-fold relative to disease-free population[35]. Both CP and PDAC share a common pathological feature – abundant desmoplastic and inflammatory stroma[36]. Hence, the link between the former and the latter could be attributed to the events occurring in the surrounding inflammatory milieu. This was proven in an animal study involving the insertion of K-ras oncogenes within the endogenous K-ras locus, in which mice without pancreatitis did not develop PDAC, while those with pancreatitis did[37]. Thus, it could be deduced that inflammation is a critical factor in PDAC carcinogenesis, at least in response to this, the commonest of oncogenes implicated in pancreatic cancer. In chronic pancreatitis, the release of inflammatory cytokines such as TNF-α and TGF-β and growth factors such as vascular endothelial growth factor (VEGF) and PDGF trigger the proliferation of fibroblasts and the activation of pancreatic stellate cells (PSC) towards a more myofibroblast-like phenotype[38,39]. Activated PSC have a number of functions, including sustaining proliferative signalling in pancreatic epithelial cells; the release of growth factors; and the synthesis of ECM proteins, notably collagen, fibronectin and laminin[40,41]. The deposition of various ECM proteins could cause a perturbation in the dynamics of the ECM, potentially damaging the genome surveillance machinery of normal epithelial cells. Supportive of a role for certain ECM components in PDAC progression is the finding that collagen 1, 4 and hyaluronic acid which promotes cell survival, proliferation and invasion, with higher levels associated with reduced survival[42-44]. This is further supported by the therapeutic benefit derived from the administration of PEGylated Recombinant Human Hyaluronidase in addition to chemotherapy in PDAC patients[45,46].

Table 1 Summary of various inflammatory and fibrotic conditions and relevant malignancies

Disease	Associated cancer	Mechanism	Risk ratio	Possible therapeutic targets
Inflammatory bowel disease	Colorectal cancer	Increased pro-inflammatory cytokines (TNF-α, IL-6 and TGF-β)[24,30,34]; Increased signalling of pro-tumorigenic molecular pathways, apoptosis resistance, fibrogenesis (NF-κB and Wnt/β-catenin)[9,27,30,34]	Ulcerative colitis – 4.8-fold increase[13]; Crohn's disease – 2-3-fold increase[17]	Thiopurines[173] and anti-inflammatory such as mesalazine [174] and NSAID[149]
Chronic pancreatitis	Pancreatic ductal adenocarcinoma	Increased cytokines (TNF-α and TGF-β), growth factors (VEGF, PDGF)[38]; Fibroblast and pancreatic epithelial cell proliferation[40]; Activation of pancreatic stellate cells [39,40]; Increased ECM protein (collagen 1 and 4, laminin, fibronectin) and hyaluronic acid deposition[38]	20-fold increase[35]	PEGylated Recombinant Human Hyaluronidase[45,46]; NSAID[149]
Idiopathic pulmonary fibrosis	Lung cancer	Cellular morphological abnormalities (metaplasia, dysplasia) in fibrotic areas[59]; Reduced immune expression (monocytes, lymphocytes, macrophages) in fibrotic areas[50]; Mutations in tumour-suppressor genes [54]; Upregulated gene expression of ECM components such as collagen and MMP (MMP9 and 11)[57]	3.5-7.3 fold increase [51]	Anti-fibrotic drugs (pirfenidone and nindetanib)[175]
Pneumoconiosis	Lung cancer	Silicosis: Chronic increased release of pro-inflammatory cytokines (IL-12, IL-23 and TNFα) results in DNA damage [66]; Immunosuppression through increased expression of inhibitory immune markers (PD-1, LAG3, FOXP30)[70]. Asbestosis: Increased inflammation (IL-1*β*, TGF-β and PDGF) and fibrosis through expression of NLRP3[70]; Increased ROS and RNS[64,68]; Increased expression of proliferation signalling pathways (EGFR-ERK)[73]	Silicosis – 3-fold increase[15]; Asbestosis – 1.5-6.8-fold increase[65,65]	Anti-fibrotic drugs (pirfenidone and nindetanib)[152]
TB	Lung cancer	Upregulation of anti-apoptotic protein expression *via* inflammatory cytokines (TNF-α and IL-6)[59,76,78]	Pneumonia – 1.4-fold increase[14]; TB – 1.9-fold increase[14]	NSAID[176]
Liver cirrhosis	Hepato-cellular carcinoma	Cellular proliferation, telomere shortening *via* inflammatory cytokines (TGF-β, TNF-α and interleukins)[83,84]; Genomic instability (p53, Ras, mTOR, Wnt signalling pathways)[11,84]; Reduced expression of CD4+ and CD8+ cytotoxic T cell[85]; Increased regulatory T-cell response [86]; Activation of hepatic stellate cells increase myofibroblast and ECM production[11,87]; Hypoxia in fibrosis leads to genotoxicity (ROS, RNO) and angiogenesis (VEGF)[92]	Hepatitis B related – 1.17-fold increase [81]; Hepatitis C related - 1.15-fold increase[81]; NAFLD-related – 1.6-23.7-fold increase[161]	LOX/LOXL2 inhibitors[161,162]; NSAID, Pentoxifylline [177,178]
Primary biliary cholangitis	Cholangiocarcinoma	Increased proliferative signalling *via* inflammatory cytokines (IL-1β, IL-6 and HGF)[96-98]; IL-6 activates p38-MAPK, increases DNA methyltransferase (DNMT) Mcl-1 and telomerase expression[96]; DNA damage (BRAF, K-ras, cyclin d-1, c-myc, COX-2 and p53) due to dysregulated NO production[98]; Fibroblast proliferation and ECM production (collagen type 1 and 3)[103]	9-fold increase[94]	Natural anti-inflammatory products (Curcumin)[102]
GERD and Barrett's oesophagus	Oesophageal cancer	Increased inflammatory cell recruitment (macrophages T, B, dendritic cells)[107]; Inflammatory cytokine release (TNF-α, IL-6, IL-1β, IL-8) activates pro tumorigenic signalling pathways (NF-Kb, STAT-3, HIF-1a)[107,108]; Reduced immune response due to immunosuppressive cytokines (IL-10)[112]; Oxidative stress (ROS and RNS) induce mutagenesis of oncogenes and tumor suppressor genes[110]	30-125-fold increase [106]	NSAID[149]
OSF	Oral squamous cell carcinoma	Increased inflammatory cell recruitment[118]; Oxidative stress induces p53 mutation, decreased DMNT and increased HSP70 and MDM2-P2 promoter[120,122]; Increased prostaglandins, cytokines and growth factors (IL-6, TNF-α, PDGF and TGF-β)[118,119]; Fibrogenesis *via* IL-6 and TGF-β leads to increased ECM protein production (collagen, fibonectin) and inhibit ECM breakdown (PAI-1, TIMP)[124,125]; OSF-associated fibroblast promote dysplastic keratinocyte proliferation *via* GRO-α release and EGFR/ERK activation[128]	19-fold increase[114]	Anti-oxidants, steroids and hyaluronidase [178]
Physiological breast stromal density, breast conditions – chronic mastitis, sclerosing adenosis	Breast cancer	Mammographically dense breast have higher ECM proportion (collagen, immune cells)[131,133]; Mammographically dense breast have higher proportion of glandular epithelial components and lower proportion of adipocytes[132-134]	Physiological higher MBD: 4-6-fold increase[130]; Chronic mastitis: 3-fold increase[137]; Sclerosing adenosis: 2-fold increase[138]	Anti-estrogens (tamoxifen, raloxifene, exemestane and anastrozole)[154-157]; NSAID[149]; LOX-like inhibitors[159,160,163]

GERD: Gastroesophageal reflux disease; OSF: Oral submucosal fibrosis; TNF-α: Tumor necrosis factor-alpha; TGF-β: Transforming growth factor beta; NF-κB: Nuclear factor κB; VEGF: Vascular endothelial growth factor; NSAID: Anti-inflammatory; GRO-α: Regulated oncogene-α; MBD: Mammographic breast density; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal–regulated kinase; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; TB: Tuberculosis; ECM: Extracellular matrix; PDGF: Platelet-derived growth factor; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; HGF: Hepatocyte growth factor; NO: Nitric oxide; BRAF: Proto oncogene B-Raf or v-raf murine sarcoma viral oncogene homolog B1; COX-2: Cyclooxygenase-2; NAFLD: Non alcoholic fatty liver disease.

However, certain alterations in the ECM can be tumour-inhibitory rather than promoting. Quantitative analysis of stroma density in PDAC samples from patients' autopsy revealed that tissue stroma density was substantially lower in samples from patients with metastatic PDAC and that higher stromal content was associated with a more favourable outcome[47]. This finding was further supported by Rhim *et al*[48] who demonstrated that diminished stromal density induced by knocking out sonic hedgehog in an established PDAC mouse model significantly enhanced tumour vascularity and proliferation. Furthermore, another study by Erkan *et al*[49] in which resected PDAC tumors were analysed for PSC activity and collagen deposition showed that the combination of high collagen deposition and low stromal activity was associated with a better prognosis than low collagen deposition and high stromal activity. While these studies relate to the effect of stroma on tumour progression/regression, considering the similarities between carcinogenesis and organ development, it is likely that these findings apply to PDAC carcinogenesis. Combining findings from these studies, the role of chronic inflammation and fibrosis in influencing PDAC risk remains ambiguous.

INTERSTITIAL LUNG DISEASE AND LUNG CANCER

Idiopathic pulmonary fibrosis (IPF) is the most common subtype of interstitial lung disease which is characterised by aberrant accumulation of fibrotic tissue in the lung parenchyma[50]. While the pathophysiology of IPF remains to be fully elucidated, the disease is thought to be mainly fibrosis-driven with minimal involvement of inflammation cascade[50]. Over the past decade, many studies have shown that IPF is linked to development of lung cancer, with a relative risk of 3.5-7.3 compared to healthy population[51]. One of the main reasons for this association is that IPF and lung cancer could have similarities in their pathophysiology, in terms of cellular morphological anomalies, dysregulated cytokine signalling and genetic mutations[52]. A study by Kawasaki *et al*[53] established that morphological aberrations in the lung epithelial layer, ranging from metaplasia and dysplasia to carcinoma, have been identified in fibrotic lung regions of IPF patients. This could be related to microsatellite instability and loss of heterozygosity, including mutations in tumour-suppressor genes such as fragile histidine triad gene, that are present at higher frequency in lung epithelial cells of IPF patients relative to healthy population[54,55]. Genetic alterations like these could be attributed to fibrosis, mainly mediated by TGF-ß released by various immune cells, and other changes in the stroma in IPF patients[56]. Using publicly available datasets, Saito *et al*[57] confirmed that 10% of the genes upregulated in lung cancer stroma, which include those coding for ECM components, mainly collagen (COL1A2, COL3A1, and COL5A2), and matrix metalloproteinases (MMP9 and 11), are also elevated in IPF. Furthermore, while increased immune cell infiltrates releasing cytokines, which promote epithelial proliferation and resist apoptosis are noted in the early stages of IPF, reduced number of lymphocytes, macrophages and monocytes were reported in fibrotic-predominant areas compared to epithelial-predominant ones in the later stages[57-61]. This implies that lung epithelial cells undergoing malignant transformation in the former are more likely to evade immune surveillance and progress to invasive malignancies in the latter. This observation concurs with the fact that lung cancers associated with IPF tend to develop in the peripheral and lower lobes – the fibrotic-predominant regions[62].

While IPF is mainly driven by fibrosis, other subtypes of ILD such as pneumoconiosis involve an inflammatory-driven condition that has been associated with lung cancer[50,63,64]. Patients with silicosis and asbestosis are about 3 times and 1.5 times more likely to develop lung cancer than the general population[15,65]. Chronic inflammation triggered as a result of the continuous activation of macrophages in an attempt to clear the silica particles is thought to mediate lung carcinogenesis in patients with silicosis[63]. Consequently, there is massive release of cytokines such as IL-12, IL-23, and TNFα which place lung epithelial cells at an increased risk of DNA damage and thus their susceptibility to malignant transformation[66]. This is demonstrated unequivocally by Wang *et al*[66] in Gprc5a-knockout mice exposed to silica where neoplastic epithelial cells were found in areas of intense lung damage and fibrosis which were thought to be a consequence of chronic inflammation. Furthermore, Freire *et al*[67] demonstrated increased lung adenocarcinomas in mice treated with the combination of the carcinogen N-nitrosodimethylamine and silica. On histopathological analysis, there was increased expression of various inhibitory immune markers including programmed cell death protein 1, lymphocyte-activation gene 3, and forkhead box P3, as well as the presence of regulatory T cells in mice treated with NMDA and silica compared to silica alone[67]. This produces marked immunosuppression which increases the risk of carcinogenesis, providing another plausible explanation for the link between silicosis and lung cancer.

Similarly, in the case of asbestosis – linked with a 6.8-times and increased incidence of lung cancer respectively compared with the general population – the pathogenesis by which it causes malignancy appears to be a combination of inflammation and the direct genotoxic effect of asbestos fibres on the genome[68,69]. Alveolar macrophages have been known to play a major role in handling asbestosis fibres[68]. The entrapment of asbestos stimulates the activation of NOD-like receptor family, the pyrin domain containing 3 expressed in alveolar macrophages which promotes the activation of IL-1*β*, along with other cytokines such as TGF-β and PDGF which are responsible for the formation of

fibrotic nodules[68,70]. In addition, macrophages increase the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby stimulating genotoxicity, chronic inflammation and thus malignancy transformation[71]. More specifically, numerous studies have demonstrated that chronic inflammation as a result of asbestos exposure affected several cell signalling pathways that are likely responsible for the development of lung cancer including the epidermal growth factor receptor (EGFR)-related extracellular signal–regulated kinase (ERK) signaling that promote lung epithelial cell and fibroblast proliferation[71-73]. While these studies have established the effect of chronic inflammation on development of lung cancer and mesothelioma, there is still a need to ascertain the relevance of fibrosis and lung cancer in vivo.

PNEUMONIA, TUBERCULOSIS AND LUNG CANCER

Infections of the lung have been previously linked with the future development of lung cancer. A meta-analysis by Brenner *et al*[14] demonstrated that pneumonia and tuberculosis was linked with a 1.4- and 1.9-times increased risk of developing lung cancer in the future. While both pneumonia and tuberculosis constitute as infection of the lung parenchyma, the degree of pulmonary inflammation and subsequent fibrosis likely explains the variation in the risk of developing lung cancer[14]. In regards to the former, pulmonary inflammation occurs for a shorter duration and thus the resulting fibrosis is less if not negligible compared to the latter, where a significant level of inflammation and fibrosis is involved[74,75]. Furthermore, in the setting of further tuberculosis (TB) recurrences which can occur in up to 47% of TB patients, repeated inflammatory response will increase the risk of lung cancer each time, with high cumulative risk associated with more frequent recurrences[76,77]. The mechanism by which inflammation increases cancer risk relates to the action of ROS and RNS produced by immune cells on the genome of lung epithelial cells and the ability of pro-inflammatory cytokines such as TNF-α and IL-6 to upregulate the expression of anti-apoptotic proteins[76,78]. Additionally, recurrent bouts of inflammation results in fibrosis in the surrounding lung parenchyma, which increases the risk of cancer associated with poor lymph drainage[79]. Further supporting the link between inflammation and lung cancer risk is a meta-analysis by Khuder *et al*[80] which demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) conferred a protective benefit in reducing lung cancer risk following adjustment for smoking (OR: 0.68; 95%CI: 0.55–0.85). These studies reaffirm the association between inflammation, fibrosis and lung cancer risk.

LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

The link between hepatic cirrhosis and hepatocellular carcinoma (HCC) is well-established, with the 5-year HCC cumulative risk of 17% and 15% respectively for hepatitis B-related and hepatitis C-related cirrhosis respectively[81]. NAFLD-related cirrhosis is also associated with the development of HCC, with multi-centre cohort studies showing 1.6 to 23.7 times increased risk[82]. Chronic inflammation and fibrosis are thought to be the major mechanisms explaining this association. In chronic hepatitis, a multitude of immune cells release various cytokines, most notably, TGF-β, TNF-α and interleukins, which lead to an increase in cellular proliferation, telomere shortening and genomic instability involving signalling pathways such as mechanistic target of rapamycin and Wnt signalling[83,84]. Additionally, previous studies revealed that CD4+ cells – involved in activation of the tumour-killing CD8+ cytotoxic T cells – and regulatory T cells – responsible for suppressing immune response – are diminished and increased respectively in cirrhosis[85,86]. Furthermore, chronic inflammation leads to fibrosis. Specifically, TGF-β released by Kupffer cells (macrophages) promote the activation of quiescent hepatic stellate cells (HSCs), analogous to PSCs in the pancreas, becoming myofibroblasts which are the primary source of ECM proteins including collagen, undulin, fibronectin and elastin[11,87]. More recently, others have identified additional cytokines, growth factors and lipid signals produced by other stromal components including endothelial cells, Kupffer cells and adipocytes are involved in HSC activation[88-90]. Fibrosis impairs the hepatic vasculature and produces a hypoxic environment, triggering the production of reactive oxygen, nitrogen species (ROS and RNO). ROS and RNO in turn can cause oxidative DNA damage among hepatocytes, predisposing them to malignant transformation[91]. Additionally, hypoxia induces the transcription of pro-angiogenic factors such as VEGF which is responsible for angiogenesis[92]. Further exacerbating this tumorigenic environment, neo-angiogenesis promotes the recruitment of immune cells like macrophages which results in further inflammation driving a vicious cycle. Today, the relationship between cirrhosis and HCC is extremely robust, that liver stiffness, a hallmark of hepatic cirrhosis is being studied as a means of assessing HCC risk[93].

PRIMARY BILIARY CHOLANGITIS AND CHOLANGIOCARCINOMA

Primary biliary cholangitis (PBC) is one of the most common risk factors for cholangiocarcinoma, with ninefold increased risk of developing cholangiocarcinoma[94]. The pathogenesis of cholangiocarcinogenesis in patients with PBC is multifactorial. Apart from the biliary constituent in PBC patients, chronic inflammation involving cytokines and growth factors, notably IL-6, hepatocyte growth factor, and IL-1β, released by various stromal and immune cells have been implicated in sustaining proliferative signalling in biliary cells[95-98]. IL-6 is believed to be a predominant contributor in cholangiocarcinogenesis, with the potential to promote cellular proliferation, survival and immortalisation *via* different mechanisms – p38MAPK activation[99], increasing DNA methyltransferase[96], Mcl-1 and telomerase expression[100]. In

addition, the inflammatory milieu in the surrounding bile duct raises the production of NO which increases the probability of DNA damage, affecting genes such as BRAF, K-ras, cyclin d-1, c-myc, COX-2 and p53[98,101]. Using a hamster model of cholangiocarcinoma, Prakobwong *et al*[102] demonstrated a decrease in incidence of cholangiocarcinoma, accompanied by decline in pro-inflammatory, growth signalling and anti-apoptotic protein expression including COX-2, cyclin-d1, c-myc, bcl-2 and bcl-xL following administration of curcumin, traditional anti-inflammatory agent derived from turmeric. This highlights the crucial role of inflammation in cholangiocarcinogenesis. Thirdly, fibrosis, instigated by the release of cytokines like IL-6 and TGF-β by immune cells, has also been shown to be involved in the neoplastic transformation of biliary cells. Using a liver cirrhosis mouse model, Farazi *et al*[103] showed that increased levels of fibroblasts along with type 1 and 3 collagen stimulate intrahepatic cholangiocyte proliferation and subsequent malignant transformation in p53-deficient mice. In another study, Ling *et al*[104] demonstrated that cholangiocarcinoma was induced in a rat model of thioacetamide (TAA)-induced hepatic fibrosis. The association between inflammation, fibrosis and cholangiocarcinogenesis is sufficiently convincing to stimulate interest in agents such as curcurmin that may diminish the two are being investigated to reduce the risk of cholangiocarcinoma[102,105].

GASTROESOPHAGEAL REFLUX DISEASE, BARRETT'S OESOPHAGUS AND OESOPHAGEAL CANCER

For a long time, chronic gastroesophageal reflux disease (GERD) patients have been known to be at risk of oesophageal cancer (OC), with 10%-20% developing Barrett's oesophagus (BO), making them 30-125 times more likely than the general population to develop OC[106]. Unlike HCC and cholangiocarcinoma where fibrosis is thought to be crucial to carcinogenesis, the pathophysiology of OC is inflammation-predominant. In GERD patients, chronic inflammation and oesophageal injury initiated by reflux of gastric acid bile and salt, result in BO, which is an intermediate step to progression to OC. More specifically, reflux promotes the recruitment of inflammatory cells, notably macrophages T, B and dendritic cells which release various pro-inflammatory cytokines such as TNF-α, IL-6, IL-1B and IL-8 that are responsible for NF-Kb, STAT-3, and HIF-1a activation[12,107,108]. This in turn leads to cellular proliferation and de-differentiation as part of a metaplastic process, a frequent precursor to neoplastic transformation. Further, immunosuppressive cytokines, notably IL-10 are found at higher levels in BO, and thus, could render healthy squamous epithelial cells undergoing malignant transformation less susceptible to destruction as a result of immune surveillance[109]. Furthermore, chronic inflammation creates a state of oxidative stress, evident by the increased levels of ROS and RNS present in BO[110]. The heightened level of oxidative stress in turn induces mutagenesis of oncogenes and tumour-suppressor genes, including TP53, K-ras, FBXW7 and PI3KCA, thereby contributing to OC carcinogenesis[110]. While chronic inflammation contributes significantly to OC carcinogenesis, the role of other aspects of stroma, including fibrosis on OC carcinogenesis remains unexplored. Interestingly, fibrosis is not apparent in BO, hence providing evidence of an inflammatory condition increasing cancer risk without the need for progression to fibrosis. Considering the reverse situation, we can hypothesise regarding the role of fibrosis on carcinogenesis from studies on eosinophilic oesophagitis, where both inflammation and fibrosis are prominent features but were not found to be associated with increased risk of OC[111]. Several mediators appear to be involved in this fibrosis, namely TGF-β, Th-2 type cytokines and ROS[112,113]. We could hypothesise that fibrosis may suppress neoplastic transformation in this scenario[111]. At this stage, while chronic inflammation substantially elevates OC cancer risk, fibrosis may have differing context specific effects on OC risk.

ORAL SUBMUCOSAL FIBROSIS AND ORAL SQUAMOUS CELL CARCINOMA

Apart from tobacco smoking, oral submucosal fibrosis (OSF) is the major risk factor for the development of oral squamous cell carcinoma (OSCC), increasing the likelihood by up to 19-fold compared to a healthy population[114]. The aetiology for OSF has long been established, with increasing incidence attributed to daily consumption of areca nut and betel quid[115,116]. In addition to the carcinogenic potential of constituents of areca nut and betel quid on activating oncogenes and inhibiting tumour-suppressor genes, they are also known to be inflammatory[117]. This promotes the recruitment of immune cells, predominantly, macrophages, T cells and lymphocytes to the oral mucosa, which in turn release ROS, prostaglandins, cytokines and growth factors, notably IL-6, TNF-α, PDGF and TGF-β[118]. These biological mediators, present in the surrounding oral squamous epithelium, promote oral squamous cell proliferation and survival [118]. Additionally, ROS promotes oxidative damage and mutagenesis, resulting in p53 mutations, decreased levels of DNA-methyltransferase repair enzyme and upregulated levels of HSP70 and MDM2-P2 promoter, which ultimately lead to neoplastic transformation in areas of OSF[119-123]. Interestingly, some of the aforementioned biological mediators, namely IL-6 and TGF-ß are significantly involved in fibrogenesis – synthesising ECM proteins like collagen and fibronectin and simultaneously producing plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitor of metalloprotease which inhibit ECM breakdown[124-126]. This produces extensive fibrosis, particularly in the lamina propria, a hallmark feature of OSF. Recently, in an immunohistochemical study involving tissues obtained from patients with normal mucosa and OSF, Gadbail *et al*[127] demonstrated that Ki67 expression, a marker for cell proliferation, was directly proportional to α-SMA expression, a marker for myofibroblast formation, potentially highlighting that fibrosis may be directly involved in neoplastic transformation. The effect of fibrosis on malignant transformation of oral squamous epithelial cells is further stressed in an *in-vitro* study by Ye *et al*[128], who showed that growth-regulated oncogene-α from OSF-associated fibroblasts promote dysplastic keratinocyte cell line proliferation *via* activation of the EGFR/ERK signalling pathway. The potential of inflammation and fibrosis in OSF to cause neoplastic transformation to OSCC is regarded as high, justifying the ongoing search for anti-inflammatory and anti-fibrotic agents to suppress these

processes in OSF[76,129].

BREAST CANCER, PHYSIOLOGICAL MAMMOGRAPHIC DENSITY, PATHOLOGICAL INFLAMMATION AND CANCER RISK

Up to this point the breast appears to be a unique case in considering links between stromal composition and cancer risk. The differentiator is the strong established link between mammographic breast density (MBD), as assessed on mammographic images, which ties to the stromal composition of the normal breast, and breast cancer risk. Women with MBD lying in the highest quartile have a 4-6-fold higher risk of developing breast cancer than those in the lowest quartile [130,131]. Dense tissue has been found to correlate with higher proportions of ECM, particularly collagen[132], immune cells[133] and glandular epithelial components, and lower proportions of adipocytes[134]. As well as promoting initial carcinogenesis, higher mammographic density has been found to correlate with a higher risk of local relapse, a lower rate for complete response to chemotherapy[135] and a higher rate of relapse after treatment in locally advanced tumours [136].

This raises the question as to whether higher 'physiological' tissue stromal density carries higher risks of cancer in other organs, as well as whether pathological inflammatory and fibrotic processes impact cancer risk in the breast. Considering the latter, inflammatory conditions that result in a sustained inflammatory environment in the breast are relatively rare. Chronic mastitis is a condition whereby there is sustained inflammation usually relating to chronic infection. A retrospective cohort study by Chen *et al*[137] revealed that patients aged ≥ 40 with a history of mastitis have 3-fold increased risk of developing breast cancer aHR = 3.71, 95%CI = 1.9–7.02) compared to those without a history of mastitis. On the same note, fibrotic condition of the breast such as sclerosing adenosis has also been associated with an approximate doubling of breast cancer risk in a US retrospective cohort[138]. This further highlights the significance of inflammation and fibrosis in influencing cancer risk and emphasises consideration of more rigorous screening for these conditions and therapeutics which could manipulate the stroma and reduce cancer risk.

STROMAL MANIPULATION TO THERAPEUTIC ADVANTAGE

The abundant evidence for multiple robust links between inflammation, fibrosis and carcinogenesis (Figure 1), as well as the frequently overlapping spectrum of implicated signalling mediators and pathways, suggest that there may be substantial therapeutic benefit to be achieved by detecting and targeting these processes across many cancer types (Table 1).

Knowledge of the links between inflammation and malignancy are widely exploited in the screening of at-risk individuals with a variety of conditions. First there is promise in the assessment of stromal characteristics to predict cancer risk, thereby allowing identification of individuals suitable for screening or for whom screening could be adjusted. For instance, the strong relationship between MBD and breast risk has been described above. Initiatives are already in progress to use MBD levels to tailor screening, both considering the age at which to start screening and the frequency as well as whether other modalities should be considered such as ultrasound or MRI[139,140]. Additionally, robust link between liver cirrhosis and HCC has prompted surveillance quantification of alpha-feto protein and liver as a means to diagnose HCC earlier[141]. Furthermore, there are screening recommendations for patients with BO and IBD to undergo surveillance gastroscopy and colonoscopy to detect the relevant malignancies at early stages[142,143].

Beyond detection, the common mechanisms underlying links between tissue inflammation, fibrosis and malignancy have led to development of a number of strategies to target these underlying processes including the application of therapeutics including anti-proliferatives, anti-inflammatories, anti-estrogens and anti-fibrotics which will be discussed below.

Anti-proliferative

Thiopurines (azathioprine, mercaptopurine and thioguanine) has been a mainstay drug for IBD patients over the last 50 years. Its main drug effect is derived from the production of its metabolites 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP)[144]. These metabolites exert an immunosuppressive and anti-proliferative effect by binding Ras-related C3 botulinum toxin substrate 1 (Rac1) to thioguanosine triphosphate thus mitigating chronic gut inflammation in IBD. This blockade of Rac1 signalling results in decreased anti-apoptotic protein Bcl-xL expression and subsequent promotion of pro-inflammatory T-cell apoptosis[145,146]. A meta-analysis by Zhu *et al*[147] involving 95397 IBD patients, found that thiopurine use is associated with reduced risk of colorectal neoplasia (case control OR = 0.49, 95%CI: 0.34–0.70; cohort RR = 0.96, 95%CI: 0.94–0.98). While effective as a chemopreventive agent, thiopurine use should be balanced with potential adverse effects such as risk of myelosuppression and in the long term, development of lymphoproliferative disorders[146,148].

Anti-inflammatory

NSAID used widely in the treatment of chronic pain syndromes have been studied as a chemopreventive agent in a wide range of cancers. NSAIDs reduce inflammation by reversibly and non-selectively inhibiting cyclooxygenase (COX) enzymes which in turn lead to decreased production of prostaglandins and leukotrienes, mediators which have been implicated in carcinogenesis. A meta-analysis by Qiao *et al*[149] comprising of 218 studies demonstrated that aspirin use

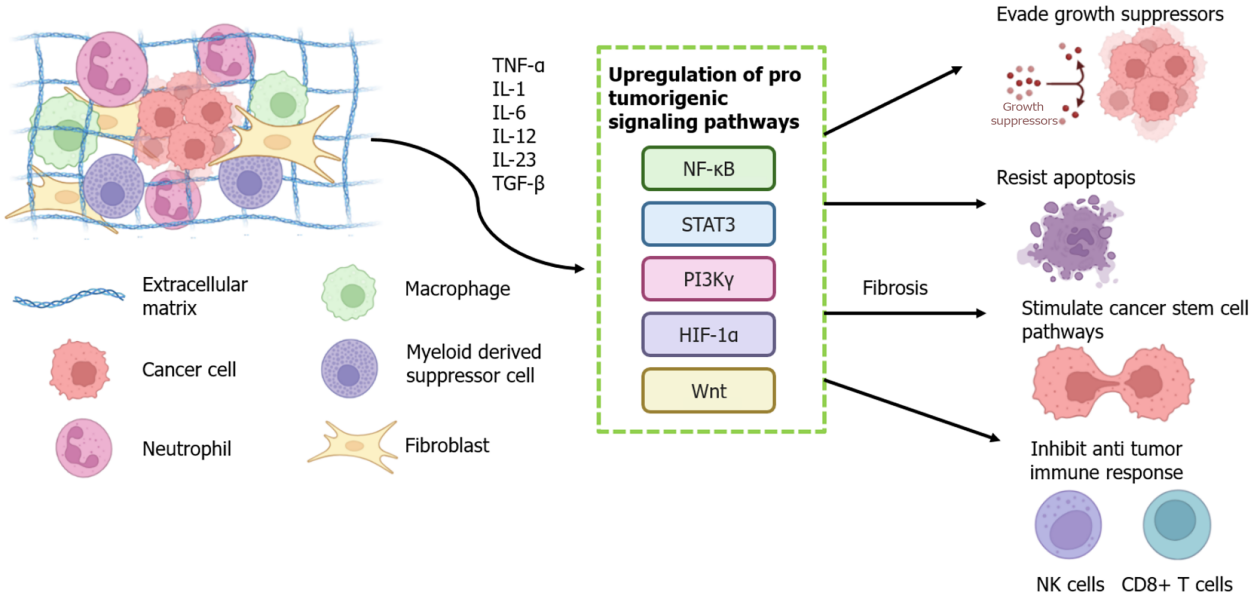

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Figure 1 Schematic showing the links between inflammation, fibrosis and cancer in the tumour microenvironment. NK: Natural killer; HIF-1α: Hypoxia-inducible factor 1alpha; PI3K: Phosphatidylinositide 3-kinase; STAT3: Signal transducer and activator of transcription 3; NF-κB: Nuclear factor qB; Wnt: Wingless-related integration site.

was associated with a significant reduction in risk of gastric, esophageal, colorectal, pancreatic, ovarian, endometrial, breast and prostate cancer with rates ranging from 6%-25%. Another meta-analysis investigating the link between NSAID and skin cancer risk has also shown positive results, with significant reduction in risk of developing basal cell carcinoma, squamous cell carcinoma and non-melanoma skin cancer, but not melanoma. Interestingly, no significant chemopreventive effect is observed for COX-2 selective-NSAIDs and NSAID use among European populations[150].

5-aminosalicylates (5-ASA) is a drug class with anti-inflammatory and immunosuppressive properties, generally utilized in treatment of IBD and various rheumatologic conditions which has recently been found to possess chemopreventive properties. It works *via* multifactorial mechanisms but two well-understood mechanisms are the inhibition of prostaglandins and leukotrienes synthesis and scavenging of reactive oxygen species[151]. Previous systematic review of 31 independent observational studies in IBD has demonstrated that 5-ASA use is associated with a 43% reduction in risk of colorectal malignancy among patients with IBD. Of note, the reduction in risk of colorectal malignancy of 50% was more prominent in UC as compared to CD, where the risk reduction was non-significant. Furthermore, the incidence of IBD-related colorectal cancer have significantly declined in recent years and whilst numerous factors could cause this, the role of 5-ASA and other immunomodulatory agents are likely to have contributed to the decrease in cancer incidence[13].

Anti-fibrotic

Nintedanib and pirfenidone are two anti-fibrotic agents which have been approved for the management of IPF. Both work *via* modulation of fibrogenic growth factors, thereby decreasing fibroblast proliferation, myofibroblast differentiation, collagen and fibronectin synthesis, and extracellular matrix deposition[152]. Recent retrospective study by Naoi *et al*[153] demonstrated that the cumulative incidence of lung cancer in patients with IPF treated with antifibrotic agent was significantly lower than those who were not (2.2% *vs* 4.4% at 1 year, 2.2% *vs* 6.7% at 3 years, and 3.3% *vs* 9.7% at 5 years, respectively; $P = 0.004$)[153]. Interestingly, the use of anti-fibrotic agent was also associated with lower lung-cancer related mortality (1.6% *vs* 15.2%, respectively; $P = 0.0001$)[153]. With established benefits in terms of slowing progression, possibly improving survival in IPF and more recently, preventing lung cancer development, the use of anti-fibrotic agents should be strongly considered in all IPF patients provided that there are no contraindications.

Anti-estrogens in breast cancer

Anti-estrogens inhibit the synthesis or antagonise action of estrogen in target organs. Anti-estrogens encompass selective estrogen receptor modulators (SERMs), selective estrogen receptor degrader, aromatase inhibitors, gonadotrophin release hormone agonists and antagonists. Previous studies have shown that tamoxifen, raloxifene, exemestane and anastrozole have significantly reduced the incidence of breast cancer in high-risk women by 49%[154], 76%[155], 65%[156], 49%[157] respectively. Currently, two SERMs, tamoxifen and raloxifene, are approved by the FDA for breast cancer chemoprevention, with anastrozole and exemestane pending approval. The mechanism of action by which antiestrogens prevent breast cancer remains unclear, however, the reduction of breast stromal density brought about by antiestrogen use is thought to confer a less pro-tumorigenic environment and hence lowering breast cancer risk.

Stromal disruption

Lysyl oxidase (LOX) and LOX-like inhibitors are another drug class targeting the stroma of immense chemopreventive potential. LOXL is amine oxidase which catalyse the cross-linking of collagen and elastin in normal tissue and extracellular matrix, facilitating carcinogenesis, cell proliferation, migration and metastases[158]. Whilst previous studies have mainly investigated LOXL inhibitors as an anti-cancer agent, the preliminary results have been promising and LOX role in carcinogenesis make it a particularly interesting target to prevent carcinogenesis. Anti-GS341, antibody targeting LOXL-2 has been shown to significantly reduce tumour volume and lung metastases in a breast cancer xenograft model using MDA-MB-231 cells into immunocompromised SCID mice[159]. Additionally, an orally bioavailable LOX/LOXL2 inhibitor, CCT365623, developed by Leung *et al*[160] produced significant diminution in tumor growth and metastases in an in vivo model of transgenic LOX-dependent breast tumor mice[160]. These promising preclinical findings have translated to clinical trials exploring LOX/LOXL inhibitor in numerous diseases including myelofibrosis, cirrhosis, and breast cancer[161-164].

Another potential stromal disruption agent targets the extracellular matrix, particularly degradation of hyaluronic acid (HA), an important component of the ECM known to participate in carcinogenesis, tumor progression and metastasis in various cancers[165]. PEGPH20 is a PEGylated human hyaluronidase that showed promise both as single agent or in combination, in numerous preclinical studies[165-167]. Thompson *et al*[168] showed that repetitive PEGPH20 administration significantly inhibited tumor growth by 70% in high-HA prostate PC3 tumors and improved both docetaxel and liposomal doxorubicin activity in PC3 tumors. Additionally, using HA synthase 3-overexpressing and wild-type SKOV3 ovarian cancer model and in the BxPC3 pancreas xenograft tumour model, Morosi *et al*[166] showed that PEGPH20 enhanced the antitumor activity of paclitaxel by modifying the tumour tissue architecture. Despite the promising potential of PEGPH20 in preclinical studies, clinical trials of PEGPH20 in various advanced solid tumours have been disappointing with PEGPH20 failing to meet its primary end point of improvement in overall survival[169]. However, it is crucial to note that PEGPH20 has not been explored in preventing carcinogenesis such as in the context of IBD, cirrhosis and IPF. Considering the significance of the ECM in carcinogenesis, future studies should study the effect of ECM-degrading agents such as PEGPH20 in carcinogenesis.

In addition to targeting the ECM, agents targeting other components of the ECM have been studied. Most notably, agents targeting myofibroblasts which produce pathological fibrosis and thus a pro-carcinogenic environment have shown promising results in previous studies. Depletion of myofibroblasts by targeting its marker, fibroblast activation protein-α, has been shown to inhibit tumor growth by augmenting anti-tumor immunity[170,171]. Additionally, agents targeting TGF-β, an important cytokine in myofibroblast activation have also been studied as TGF-β inhibition has been demonstrated to prevent myofibroblast activation and prevent immunosuppression and thus cancer progression[172]. Again while these agents are studied as anti-cancer therapies, these drugs have immense potential to be utilised as chemopreventive agents in disorders of chronic inflammation and fibrosis to prevent carcinogenesis.

CONCLUSION

In conclusion, the correlation between chronic inflammation, fibrosis and cancer risk is complex, with the former being more straightforward. Chronic inflammation in the stroma of different body tissues promotes carcinogenesis *via* different mechanisms – growth factor/cytokine-mediated cellular proliferation, apoptotic resistance and immunosuppression; and free-radical-induced oxidative DNA damage. However, certain immune cells, involved in tumour-surveillance may be depleted, as seen in IPF and hepatic cirrhosis, thereby raising cancer risk by compromising immune surveillance of tumours. The relationship between stromal fibrosis and cancer risk varies in different organs, implying that the effects of fibrosis could be tissue-specific. Increased stromal fibrosis is associated with an increased cancer risk in organs like the lung, liver, biliary tract and colorectal region. Conversely, in other organs such as pancreas and potentially, oesophagus, increased stromal fibrosis may confer a lower cancer risk.

At this current time, the mechanism by which fibrosis influences cancer risk is still ambiguous. We propose two hypotheses. Firstly, a fibrotic environment contributes to an aberration in ECM dynamics which affects normal cellular behaviour and ultimately neoplastic transformation. Secondly, we hypothesise that fibrosis may present as a safe alternative to cellular regeneration which has the potential to produce aberrant DNA mutations, resulting in tumour formation. What determines the former or the latter are a multitude of factors which could include fibroblast heterogeneity and plasticity; extent of fibrosis; inflammation; and the predominance of certain mediators over others. Therefore, future studies, especially *in-vitro* and animal studies, should investigate the mechanisms by which fibrosis contributes to carcinogenesis in various organs in further depth and determine if fibrosis, alone or only in conjunction with inflammation would promote carcinogenesis. Furthermore, the role of surveillance screening and therapeutic agents with stroma manipulation potential in patients with diseases which involve chronic inflammation and fibrosis should be further studied to reduce the incidence of relevant cancers.

FOOTNOTES

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Country/Territory of origin: Australia

ORCID number: Angela Felicia Sunjaya 0000-0001-8831-0449.

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MINIREVIEWS

Role of prophylactic central neck lymph node dissection for papillary thyroid carcinoma in the era of de-escalation

Efstathios T Pavlidis, Theodoros E Pavlidis

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Efstathios T Pavlidis, Theodoros E Pavlidis, 2nd Propedeutic Department of Surgery, Hippocration Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Corresponding author: Theodoros E Pavlidis, Doctor, PhD, Full Professor, Surgeon, 2nd Propedeutic Department of Surgery, Hippocration Hospital, School of Medicine, Aristotle University of Thessaloniki, Konstantinoupoleos 49, Thessaloniki 54642, Greece.
pavlidth@auth.gr

Abstract

Thyroid cancer is the most common endocrine malignancy. While there has been no appreciable increase in the observed mortality of well-differentiated thyroid cancer, there has been an overall rise in its incidence worldwide over the last few decades. Patients with papillary thyroid carcinoma (PTC) and clinical evidence of central (cN1) and/or lateral lymph node metastases require total thyroidectomy plus central and/or lateral neck dissection as the initial surgical treatment. Nodal status in PTC patients plays a crucial role in the prognostic evaluation of the recurrence risk. The 2015 guidelines of the American Thyroid Association (ATA) have more accurately determined the indications for therapeutic central and lateral lymph node dissection. However, prophylactic central neck lymph node dissection (pCND) in negative lymph node (cN0) PTC patients is controversial, as the 2009 ATA guidelines recommended that CND "should be considered" routinely in patients who underwent total thyroidectomy for PTC. Although the current guidelines show clear indications for therapeutic CND, the role of pCND in cN0 patients with PTC is still debated. In small solitary papillary carcinoma (T1, T2), pCND is not recommended unless there are high-risk prediction factors for recurrence and diffuse nodal spread (extrathyroid extension, mutation in the *BRAF* gene). pCND can be considered in cN0 disease with advanced primary tumors (T3 or T4) or clinical lateral neck disease (cN1b) or for staging and treatment planning purposes. The role of the preoperative evaluation is fundamental to minimizing the possible detrimental effect of overtreatment of the types of patients who are associated with low disease-related morbidity and mortality. On the other hand, it determines the choice of appropriate treatment and determines if close monitoring of patients at a higher risk is needed. Thus, pCND is currently recommended for T3 and T4 tumors but not for T1 and T2 tumors without high-risk prediction factors of recurrence.

Key Words: Well differentiated carcinoma; Papillary thyroid cancer; Prophylactic central neck dissection; Thyroid disease; Thyroidectomy; Lymphadenectomy

Core Tip: Nodal status in papillary thyroid cancer patients plays an important role in the prognosis of risk for recurrence. Preoperative evaluation is crucial for minimizing the possible risk of injury from overtreatment. Undoubtedly, therapeutic central neck dissection in addition to total thyroidectomy should be performed if there is positive lymph node involvement. The role of prophylactic central neck lymph node dissection in patients with papillary thyroid carcinoma with negative lymph nodes has been debated. It is currently recommended for T3 and T4 tumors but not for T1 and T2 tumors without high-risk prediction factors of recurrence.

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INTRODUCTION

Well-differentiated thyroid cancer is the most common endocrine malignancy, with approximately 570000 new cases annually. Furthermore, papillary thyroid carcinoma constitutes 90% of the new cases of thyroid cancer[1]. In comparison to statistics from the previous decade, there is now an over 100% increase in its incidence worldwide. This upsurge is somewhat due not only to increasing human exposure to defined incriminated factors for the development of thyroid carcinoma but possibly also to increases in health care utilization and imaging practices (ultrasound, fine needle aspiration), which can efficiently detect small asymptomatic nodules that otherwise remain undiagnosed[2,3].

The incidence of thyroid cancer reaches its peak between the fourth and fifth decade of life, with a predominance of women with a mean ratio of 4/1[4]. The overall five-year survival rate of thyroid carcinoma reaches over 95%, which could be characterized as excellent. Thus, it is one of the most amenable malignancies to treatment. The incidence of deaths in the United States is only 0.5 per 100,000 population and has not changed significantly from 1975 to 2009[5]. Despite the increasing incidence and due to widespread high-sensitivity screening practices, there is no described increase in mortality, which supports that well-differentiated thyroid cancer is in fact being overdiagnosed[6,7].

In the last version of the American Thyroid Association (ATA) guidelines, total thyroidectomy remains the preferred management method for tumors with a diameter above 4 cm or with a diameter under 4 cm but with high-risk features. It is widely established that high-risk features, including a family history of thyroid carcinoma, prior neck irradiation, extrathyroid extension, multifocality, and central lymph node involvement, with or without lateral lymph node neck involvement, require more extended surgical resections (total thyroidectomy with or without lymph node dissection)[8].

Papillary thyroid microcarcinomas are defined as papillary thyroid carcinomas (PTCs) of 1 cm or less in size. It has been reported that they are related to extremely low local or regional recurrence rates (2%-6%) and an even lower disease-specific mortality of less than 1%[9]. Since the majority of newly diagnosed thyroid carcinomas are microcarcinomas, there is growing pressure to stage the risk and minimize possible injury from the overtreatment of low-risk thyroid disease. To this effect, the American Thyroid Association indicates lobectomy as an alternative and less invasive approach in its new guidelines, as well as to minimize the major complications of total thyroidectomy, mainly hypocalcemia and recurrent laryngeal nerve palsy[8].

Lymph node metastases are common in papillary thyroid cancer, occurring in 20%–50% of patients, and they mostly occur in the central compartment of the neck (level VI). Lymph node metastases are also known to be an independent risk factor for local recurrence[10]. Lymph node dissection of the central, i.e., levels VI, VII with lateral compartments of the neck, i.e., Levels II to V will undoubtedly be recommended if there is a confirmed presence of lymph node metastases[8]. The necessity of prophylactic central neck lymph node dissection remains contested and in an ongoing controversy in the era of de-escalation.

This narrative review evaluates the role of prophylactic central neck lymph node dissection in well-differentiated thyroid carcinoma.

RESEARCH METHODS

The study was based on the data of an extensive literature review from PubMed until March 2023, focusing on the comparison of the efficacy and surgical safety of its prophylactic performance. Only full-text papers published in the English language were included. Since the aim of this review was to study the efficacy and oncological completeness of thyroidectomy with or without central neck lymph node dissection for well-differentiated thyroid carcinoma, studies for

nonmalignant thyroid pathologies were excluded.

CLINICAL ANATOMY AND EXTENT OF THOROUGH CENTRAL NECK DISSECTION

The central neck compartment is anatomically composed of level VI and the upper part of level VII. Level VI is bounded cranially by the hyoid bone, caudally by the upper margin of the sternum, and laterally by the left and right common carotid arteries. The anterior border of the superficial layer of the deep cervical fascia is the posterior margin of the sternothyroid muscle. The posterior border is the prevertebral fascia, the deep layer of the deep cervical fascia. Near the origin of the right brachiocephalic artery, which forms the lower edge, the caudal of level VI is extended to level VII. Four groups constitute the lymph nodes of the central neck compartment, *i.e.*, the prelaryngeal (Delphian), pretracheal, right paratracheal, and left paratracheal lymph nodes. Accurate central neck lymph node dissection requires imperatively meticulous complete removal of both the prelaryngeal and pretracheal regions and those of at least one paratracheal region, either left or right. In the case of the involvement of both paratracheal regions, central neck dissection should be bilateral[10].

Patients with clinical positivity for lymph node metastasis need to undergo therapeutic central neck dissection. Metastatic lymph node involvement is usually revealed either preoperatively, by ultrasound imaging, or intraoperatively by frozen section biopsy. Prophylactic central neck dissection means removal of all lymph nodes in both levels VI and VII, despite a negative preoperative diagnosis for suspected findings (cN0). The so-called berry picking, *i.e.*, the one by one excision of only the lymph nodes with the appearance of metastasis that are in the sites that are not apparently healthy, should not be considered as an option and should be avoided[11].

The resection of paratracheal lymph nodes constitutes one of the most challenging technical parts of central neck dissection because of the necessary preservation of the anatomical integrity of all crucial structures in this region, specifically the recurrent laryngeal nerve and parathyroid glands with their vascularity. The latter deals mainly with the inferior parathyroid gland, as almost 90% of cases receive blood supply from the inferior thyroid artery, which lies beneath the area, in which all contained lymph nodes are planned to be dissected. In contrast, preservation of the upper parathyroid gland is somewhat easier during paratracheal lymph node dissection, especially when its blood supply comes exclusively from the superior thyroid artery[8,10].

RISK STRATIFICATION: PREOPERATIVE EVALUATION

The last guidelines of the American Thyroid Association state that the relevant high-risk factors from the history, *i.e.*, rapid growth of nodules, sudden swallowing dysfunction, or dysphonia, must be investigated[8]. In addition, much relevant information can be obtained at the time of the patient's examination. There is agreement among authors that age equal to or more than 45 years, female sex, familial history of thyroid carcinoma, and previous neck irradiation are considered predisposing factors for developing thyroid carcinoma, as shown in Table 1[12-14].

Undoubtedly, a precise preoperative diagnosis is a necessary condition for successfully planning the operative strategy. It is imperative to examine all the central and lateral neck lymph nodes in patients with well-differentiated thyroid carcinoma preoperatively, as well as to examine the central compartment intraoperatively. The preoperative fundamental diagnostic tools include an ultrasound scan of high resolution and fine-needle aspiration cytology of all suspected nodes[15].

Determining the levels of thyroglobulin in the aspiration material from suspicious lymph nodes significantly increases the sensitivity of the whole diagnostic evaluation. The sensitivity and specificity to detect lateral lymph node metastasis are sometimes higher compared to the central compartment; the referred sensitivity of the lateral is 93.8%, which is in contrast to that of the central compartment, which is 30%[16]. This notable difference is attributed to the complex anatomy of the central compartment. The central lymph nodes are not only smaller in diameter than the lateral lymph nodes but are also located in a groove between the esophagus, trachea, and thyroid. The interpretation of ultrasound findings is undoubtedly operator dependent, and much expertise is needed. Moreover, the presence of lymphocytic thyroiditis (Hashimoto's disease) changes, which may be accompanied by inflammatory lymphadenopathy in majority of cases and may further interfere with the interpretation of the examination findings[17].

If a suspicion of extrathyroid spread exists that is accompanied by infiltration of a neighboring structure (larynx, esophagus, trachea and the main blood vessels in the neck) or if there is possible infiltration of the mediastinal and retropharyngeal lymph nodes, then a computed tomography (CT) scan of the head, neck and thorax needs to be performed. Magnetic resonance imaging of the head and neck could occasionally be a reliable alternative to CT scan; nonetheless, for the central compartment, it is less enlightening when compared to CT scan[15].

ROLE OF CENTRAL NECK NODAL STATUS

In patients with papillary thyroid cancer and clinical evidence of central with or without lateral lymph node metastases (cN1), the necessary initial treatment includes, central lymph node dissection with or without lateral neck dissection, in addition to total thyroidectomy. Level V lymph node dissection is mandatory in cases of central lymph node involvement. Additionally, it is necessary when ipsilateral with or without bilateral therapeutic lateral neck dissection,

Table 1 Papillary thyroid carcinoma, risk stratification and preoperative evaluation

No.	Parameter
1	Tumor size > 4 cm
2	Family history of thyroid carcinoma
3	Previous neck irradiation
4	Multifocality
5	Extrathyroid extension
6	Rapid growth of nodules
7	Sudden swallowing dysfunction or dysphonia
8	Age ≥ 45 yr
9	Female gender

including levels IIa, III, IV, and Vb, is required[8,10,18,19]. This is because of the pivotal role of the nodal status in patients with papillary thyroid cancer, which is mainly due to its prognostic contribution to the risk of recurrence[8]. The 2015 American Thyroid Association guidelines update, in contrast to those of 2009, more precisely determines the recommendations for therapeutic central and lateral lymph node dissection when they are clinically evident. Prophylactic central neck dissection can be considered in negative central lymph node (cN0) disease of large primary tumors (T3, T4), in clinical lateral lymph node disease (cN1b), or for staging purposes to define the plan of treatment strategy. This clarified aspect is important, as the 2009 guidelines recommended that routine level VI lymph node dissection "should be considered" in all patients undergoing total thyroidectomy for papillary thyroid cancer regardless of positive or negative nodal status[9]. This decisive statement has led to controversy, as many surgeons took it as an interpretation of the recommended surgery.

Well-differentiated thyroid carcinoma includes not only papillary but also follicular carcinomas. However, the latter has mainly hematogenous metastases and only occasional (less than 5% of cases) regional lymphatic metastases of the neck[20]. The most common locations for distant hematogenous metastases are the lungs and brain[21], with a metastasis rate that fluctuates between 6% and 20% of cases[22,23]. To this effect, there is no need for prophylactic central neck dissection in follicular cancers, except for those cases in which there are clinically evident central neck metastases.

Lymphatic metastases of papillary thyroid carcinoma are mainly located in the regional lymph nodes. They most often affect the lymph nodes of level VI (paratracheal) and, in distant time, those of the lateral neck compartment, specifically levels III and IV, and extremely rarely level I[24,25]. In the absence of central lymph node metastases, escaped lateral lymph node metastases have been reported with an overall incidence of 20%[26]. They are associated, in most cases, with carcinoma located in the superior thyroid third, which mainly has metastases in lymph node levels II and III[27]. Notably, approximately 83% of the cases with lateral lymph node involvement also have microscopic metastases of the ipsilateral central lymph nodes, and 4% of them cannot be revealed by any preoperative diagnostic tool. In this clinical scenario, a need exists for at least ipsilateral prophylactic central neck dissection regardless of the negative clinical status[28].

In 5%-10% of cases of papillary thyroid carcinoma, palpatory clinical evidence of regional metastatic disease (macroscopic disease) exists at the time of diagnosis. The use of more sophisticated diagnostic approaches, including high-resolution ultrasound with fine-needle aspiration biopsy, may increase the former incidence by up to 30%[29]. Hematoxylin and eosin staining, the classical histopathological tool, can reveal positive typical lymph nodes in 30% to 50% of patients with papillary thyroid carcinoma who underwent elective central with lateral lymph node dissection[30]. There are studies in which an additional immunohistochemical evaluation of the resection specimen revealed microscopic metastases in up to 90% of cases[31,32]. These reports sustain the aspect that papillary thyroid carcinoma in most cases is accompanied by microscopic dissemination of the disease at the time of diagnosis and does not usually exhibit clinical evidence.

ROLE OF PROPHYLACTIC CENTRAL NECK DISSECTION

The results from studies such as Tisell *et al*[33] and Barczyńsk *et al*[34] have suggested that prophylactic central neck dissection has a positive effect on patient survival, mainly by reducing the probability of locoregional recurrence. The effect of lymph node status in recurrence and survival in PTC is shown in Table 2. Such a recurrence is based on macroscopic metastases with infiltration beyond the thyroid caps, a larger number of either positive or negative nodes in the overall lymph nodes included in the performed dissection, as well as the existence of five or more nodes with metastasis in the initial specimen[35]. However, the recurrence ratio could be described as very low in the presence of microscopic metastases[36]. Although the incidence of nodal micrometastases in the central compartment ranges from 38% to 80%, the probability of local nodal recurrence is below 3.8%, and central neck dissection is either performed or not [37,38].

Table 2 Effect of lymph node status in recurrence and survival in papillary thyroid carcinoma

Ref.	Patients (Nu)	Trial	Survival
Tisell *et al*[33], 1996	195	Single center retrospective study	Increased in ≥ 45 yr; Unaffected in < 45 yr
Zaydfudim *et al*[20], 2008	30504	United States Registry, Surveillance	Increased in ≥ 45 yr; Unaffected in < 45 yr
Lundgren *et al*[38], 2006	5123	Swedish Registry Surveillance	Increased

In addition, the studies from Lundgren *et al*[38], including 5123 patients, and Zaydfudim *et al*[20], including 33088 patients, assessed the existence of metastases in the central and lateral compartments and documented a reduced survival rate. The recognized risk factors were age > 45 years in papillary cancer patients, male sex, metastases > 3 cm in size accompanied by spread beyond the thyroid caps, and the histopathological type of diffuse invasive follicular carcinoma [20,39,40]. According to the aforementioned, the selection of initial operative management has gained great importance; it should not be required to use only the tumor size as a criterion to determine the surgical plan.

Although there has been a worldwide agreement that lateral lymph node dissection should be preserved only in clinical N1b cases, the role of prophylactic central lymph node dissection in cN0 papillary thyroid carcinoma is still debated[40-45]. However, the preoperative evaluation of lymph nodes can be characterized as challenging. According to a meta-analysis from Liang *et al*[46], who included 23 "high-quality" studies, the proportion of central neck lymph node metastases fluctuates between 16.7% and 82.3% in those patients who underwent prophylactic central neck dissection.

Taking into account these broad ranges in the rate of central neck metastases, obtaining a high-quality evidence-based recommendation concerning prophylactic central neck dissection could be defined as demanding. A reason that could explain this heterogeneity in the literature's results could be the difference in the expertise of obtaining a preoperative assessment by ultrasound, the plan of surgical management, and the histopathological evaluation. The basic assertions that are in favor of prophylactic central lymph node dissection concern the better staging accuracy, a more precise allocation to radioiodine treatment and the more reduced levels of postoperative thyroglobulin, possibly contributing to a decrease in the recurrence risk[46,47].

Otherwise, the basic argument against the abovementioned is the increased potential for complications, mainly hypoparathyroidism and laryngeal nerve injury[40,48]. A more conservative approach, i.e., ipsilateral (IpsiCND) central neck dissection, provides a lower rate of complications and was proposed in patients with clinical unilateral papillary thyroid carcinoma. It includes removal of the prelaryngeal, pretracheal and paratracheal lymph nodes on the same side as the tumor[49].

Even if the preoperative evaluation of the central lymph node compartment has not confirmed nodal metastasis, it must not prevent the surgeon from sending any suspicious node for intraoperative frozen-section histopathological assessment, and the assessment should not be based only on an intraoperative clinical inspection and palpation. Depending on the outcome of the frozen-section biopsy, a decision on therapeutic central lymph node dissection can be made. Several authors have verified that the sensitivity and specificity of intraoperative frozen-section biopsy may reach 100%[50]. Nevertheless, even in experienced hands, only approximately 26% of the confirmed metastases of the lymph nodes could be revealed based only on the intraoperative clinical evaluation[51].

In consonance with the novel scientific evolution, there is no reason to perform ipsilateral prophylactic central neck dissection for small solitary (T1, T2) well-differentiated thyroid carcinomas. The incriminated factors for the development of locoregional metastases include the larger diameter thyroid carcinomas (T3, T4), multifocality, a tall cell, a diffuse sclerotic and insular tumor that represents an aggressive subtype[52-56] as well as positivity for *BRAF* gene mutations on genetic testing[57]. In such scenarios, ipsilateral prophylactic central neck dissection is recommended. Nonetheless, the majority of the aforementioned data concerning possible malignancy are available only postoperatively after a precise tumor histopathological evaluation. Unfortunately, that accurate information is not available in advance for determining the plan of the extent of operative resection, thus carrying out a prophylactic central neck dissection is ultimately required.

A reliable alternative could be a prophylactic ipsilateral neck dissection frozen section examination, as proposed by Raffaelli *et al*[58]. Taking into consideration the highly accurate rate of frozen section evaluation of the ipsilateral central lymph node compartment in assessing the nodal status of negative cases with papillary thyroid cancer (up to 90%), they hypothesized that the frozen section assessment of ipsilateral central lymph node dissection could be valuable to modulate the extension of surgical resection. Undoubtedly, if there is an occurrence of hidden ipsilateral central lymph node metastasis, then total thyroidectomy and therapeutic central compartment dissection will become mandatory. Currently, in a case control study (unpublished data), they adopted such operative tactics personalizing the extent of the attempted resection in patients with small (T1) papillary thyroid carcinoma, without both multifocality and central lymph node involvement. This evaluation included 60 patients with personalized management who were scheduled for initial lobectomy only. The results, as described, confirmed that frozen section evaluation of ipsilateral central lymph node dissection may be effective and accurate in identifying patients who could benefit from bilateral central neck dissection. Therefore, the advantages include the lower risk of recurrence and subsequently the reduced need for a second more complicated operation[58].

MORBIDITY IN ELECTIVE CENTRAL NECK DISSECTION

Another factor that supports the debate concerning prophylactic central neck dissection is the intraoperative and postoperative morbidity that accompany such a procedure. Actually, the question that arises is whether the benefits exceed the potential harm. It is well known and demonstrated that the percentage of complications, namely, recurrent laryngeal nerve injuries and hypocalcemia, is increased after total thyroidectomy in cases accompanied by central lymph node dissection[59-61].

Lee *et al*[62], including 103 patients, stated that ipsilateral central neck dissection is accompanied by fewer complications, especially temporary and permanent hypocalcemia, compared to bilateral dissection. On the other hand, a meta-analysis from Chisholm *et al*[63], including 1132 patients, supports that there is no statistically significant increase in the percentages of complications, especially when neck dissection is performed by an endocrine surgeon. Zhu *et al*[64] drew the same results after evaluating nine relevant studies including 2298 patients.

Over the last two decades, a notable increase in papillary thyroid cancer and multifocal lesions as well as the coexistence of Hashimoto's chronic thyroiditis was found. In addition, there was a gradual decrease in the papillary thyroid carcinoma sizes and subsequently an increase in micropapillary carcinoma[65]. The latter has led to controversy regarding the possible increase in lymph node metastasis reflecting central lymph node dissection. However, a recent study showed that multifocal lesions were not accompanied by a relevant increase in lymph node metastasis, but bilateral multifocality was associated with more aggressive clinical behavior and tumor histopathology. Thus, in this case, prophylactic central lymph node dissection is indicated, despite preoperative or intraoperative negative lymph node involvement[66].

The incidence of lymph node metastasis posterior to the right recurrent laryngeal nerve was estimated at 6%, making it necessary to thoroughly investigate this possibility in tumors of the lower pole that are greater than 0.5 cm in size[67]. Based on the recommendation by the American Thyroid Association for routine dissection of this lymph node[8], there is an increased risk of nerve injury and palsy in these tumors. Endoscopic thyroidectomy may offer an alternative safer approach[68].

A recent meta-analysis including 15 studies showed that total thyroidectomy with prophylactic lymph node dissection for papillary thyroid carcinoma was related to a lower local recurrence rate but a higher risk of permanent hypocalcemia and transient hypoparathyroidism than total thyroidectomy alone. There were no significant differences in transient hypocalcemia, permanent hypoparathyroidism, both temporary and permanent vocal cord paralysis, and recurrent laryngeal nerve injury[69]. The results of the above mentioned studies using routine prophylactic central neck lymph node dissection in PTC are shown in Table 3.

Hashimoto's thyroiditis may cause reactive hyperplasia of the central lymph nodes in patients with papillary thyroid cancer. Nevertheless, in this autoimmune thyroiditis, there are often false-positive findings on ultrasound, which lead to possible overtreatment and complications[70].

PRE/POSTOPERATIVE PREDICTION FACTORS-RECURRENCE

Several predisposing factors for potential central lymph node metastasis in T1-T2 papillary thyroid carcinoma have been recognized. Thus, predictive nomograms have been developed, and they can be useful in planning the extent of operative strategy[71-75].

They include age (less than 44 years), gender (male), race (white and other nonblack people), size of the tumor (larger than 10 mm), multiple focal lesions, and minimal extrathyroid extension[71].

The least absolute shrinkage and selection operator -based model includes age (equal to or more than 55 years), nodular goiter, mutations in the *BRAF* gene, and Hashimoto's thyroiditis as the most important factors[72].

The preoperative ultrasound suspicious findings (size of lymph node more than 5 mm, microcalcification, cystic degeneration, round shape, abnormal boundary, and cortical thickening) in addition to clinical data constitute another model[73]. Some statistical data of ultrasound signs are shown in Table 4[74].

Papillary thyroid carcinoma that is located in the isthmus exhibits aggressiveness and is related to poor prognosis. A nomogram including incriminated factors for metastatic lymph nodes and worse outcome (gender, age, size of malignant lesion, thyroid cap invasion, and Hashimoto's thyroiditis)[75], as for any other location of high-risk patients[76], predicts recurrence[77].

Hypervascularity in ultrasound is an independent risk factor for recurrence in papillary thyroid carcinoma[78].

The ratio of fibrinogen to neutrophile percentage has been proposed as another independent risk factor for recurrence in patients with the coexistence of papillary thyroid carcinoma and diabetes mellitus type 2[79].

Multifocality (presence of two or more foci) of papillary thyroid carcinoma was determined to be a risk factor for an increased rate of central lymph node metastasis (44.57%) and lateral lymph node metastasis (17.17%)[80].

A radiomics nomogram based on ultrasound features, sex, age, *BRAF* gene *V600E* mutation, and extrathyroid extension predicts lymph node metastasis in papillary thyroid carcinoma[81].

For stage pT1α papillary thyroid microcarcinoma, multivariate analyses have demonstrated that younger age, male sex, and subcapsular location of the lesion were predictive factors for central lymph node metastasis[82].

Based on the above mentioned studies, the main high-risk prediction factors of central lymph node recurrence in T1-T2 PTC are shown in Figure 1.

Small papillary thyroid carcinoma (equal to or less than 10 mm in diameter) was found to be a prediction factor for not detecting lymph node metastases, as shown in a recent study. Multivariate analyses have also showed that the values of

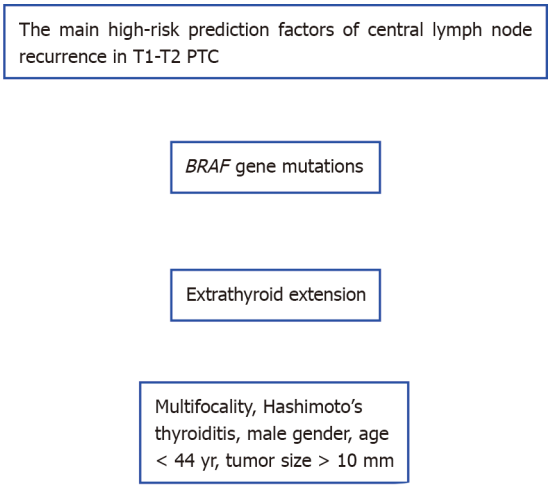
Table 3 Results of routine prophylactic central neck lymph node dissection in papillary thyroid carcinoma

Ref.	Patients (Nu)	Trial	Findings
Barczyński *et al*[34], 2013	640	Single center retrospective study	Bilateral pCND increases 10-yr disease-specific survival and locoregional control, No increased risk of permanent morbidity
Lee *et al*[62], 2007	103	Single center retrospective study	Increased transient hypocalcemia in bilateral than ipsilateral pCND
Chisholm *et al* [63], 2009	1132	Meta-analysis	No increased permanent morbidity
Zhu *et al*[64], 2013	2298	Meta-analysis	No more complications
Wang *et al* [69], 2023	2080	Meta-analysis	Reduced local recurrence; Higher risk of permanent hypocalcemia and transient hypopara-thyroidism; No significant differences in transient hypocalcemia, permanent hypopara-thyroidism, both temporary and permanent vocal cord paralysis, and recurrent laryngeal nerve injury

pCND: Prophylactic central neck lymph node dissection.

Table 4 Suspicious ultrasound findings of lymph nodes which predict malignant infiltration

Sign	Sensitivity, %	Specificity, %
Microcalcifications	5-69	93-100
Cystic degeneration	10-34	91-100
Vascularity peripheral	40-86	57-93
Hyperechogenicity	30-87	43-95
Shape round	37	70



DOI: 10.5306/wjco.v14.i7.247

Figure 1 Scheme of high-risk prediction factors of central lymph node recurrence in T1-T2 papillary thyroid carcinoma. PTC: Papillary thyroid carcinoma.

stimulated thyroglobulin are related to shorter recurrence-free survival[83]. Thus, it must be considered a reliable prediction factor for recurrence.

Despite the presence of metastasis in the lateral neck lymph nodes, dissection of the central lymph nodes is not always necessary. A multivariate analysis showed that papillary thyroid carcinoma located in the center of the lobe and fewer than 4 positive lateral lymph nodes were protective factors against central lymph node involvement, which is subsequently a positive prognostic factor[84].

Patients with papillary thyroid carcinoma and a negative preoperative investigation for central lymph node involvement and who underwent total thyroidectomy alone without planned prophylactic lymph node dissection but with an incidentally removed lymph node positive for metastasis in the specimen biopsy had a worse course and high

rate of treatment failure. In such a case, as shown in a recent large and detailed trial, the cumulative disease-free survival (DFS) was significantly lower (61.8%) *vs* 93.9%, and the cumulative survival was 79% *vs* 96% within the following 60 mo in the patients without metastasis in their incidentally removed lymph nodes[85]. Thus, a positive incidental lymph node is considered a significant risk factor for a worse outcome.

Nevertheless, the utility of intraoperative ultrasound is important for the assessment of lymph node status. Small lymph nodes (2-3 mm in size) may be evaluated adequately for metastatic spread by high-resolution neck ultrasound. The recurrence rate and subsequent need for reoperation in patients with papillary thyroid cancer and negative central lymph node involvement has been limited by the intraoperative prediction of lateral lymph nodes *via* ultrasound and their prophylactic dissection[86].

It seems from all the above mentioned that preoperative evaluation is crucial for minimizing the possible risk of injury from overtreatment in the majority of patients who otherwise have a low risk of disease-specific mortality and morbidity, whereas properly treating and monitoring those patients at higher risk is important since in some cases, nodal metastases are found in the surgical specimen. Apparently, molecular genomic assessment of diagnostic cytology samples could be more informative when dealing with the aggressive behavior of well-differentiated thyroid carcinoma to reliably modulate the extent of the initial surgery. Ipsilateral central neck dissection frozen section examination could be a reliable intraoperative method to assess the nodal status.

CONCLUSION

Although there is a clear indication for therapeutic central neck dissection according to the current guidelines, the role of prophylactic treatment in cN0 patients with papillary thyroid carcinoma is still debated. In follicular thyroid carcinoma, which usually has hematogenous metastases, there is no need for prophylactic central lymph node dissection. In small solitary papillary carcinoma (T1, T2), prophylactic central neck dissection is not recommended, as it does not provide benefits regarding prolonged survival, while this simultaneously provides a significant increase in the postoperative complication risk concerning either temporary or permanent complications, such as recurrent laryngeal nerve palsy and hypoparathyroidism. Prophylactic central lymph node dissection has been recommended in large papillary thyroid carcinomas (T3 and T4 tumors) or small ones (T1 and T2 tumors) related to high-risk prediction factors of recurrence and diffuse nodal spread, such as in extrathyroid extension or when there is a mutation in the *BRAF* gene.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Efstathios T Pavlidis 0000-0002-7282-8101; Theodoros E Pavlidis 0000-0002-8141-1412.

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ORIGINAL ARTICLE

Retrospective Study

Relationship between anal cancer recurrence and cigarette smoking

Kevin R McMahon, Nicholas Gemma, McKenzie Clapp, Patricia Sanchez-Montejo, Joseph Dibello, Erica Laipply

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Kevin R McMahon, Nicholas Gemma, McKenzie Clapp, Patricia Sanchez-Montejo, Joseph Dibello, Erica Laipply, Department of General Surgery, Summa Health System, Akron, OH 44304, United States

Corresponding author: Kevin R McMahon, MD, Doctor, Department of General Surgery, Summa Health System, 55 Arch Street, Akron, OH 44304, United States.
mcmahonkr@summahealth.org

Abstract

BACKGROUND

The incidence of anal cancer has been increasing in the United States. Smoking is a well-established risk factor; however, the impact of smoking on disease recurrence and outcome has not been well studied. The aim of this study was to assess the association between anal cancer recurrence and cigarette smoking.

AIM

To investigate the relationship between cigarette smoking status and anal cancer treatment outcome.

METHODS

The cancer registry from a single, community hospital was screened for patients with anal cancer between 2010 and 2021. The following characteristics were gathered from the database: Age; sex; cigarette smoking history; American Joint Committee on Cancer Clinical Stage Group; response to therapy; recurrence; time to recurrence; mortality; time to death; and length of follow-up. Patients were divided into the following groups: Current smokers; former smokers; and never smokers. SPSSv25.0 software (IBM Corp., Armonk, NY, United States) was used for statistical analysis.

RESULTS

A total of 95 patients from the database met the screening criteria. There were 37 never smokers, 22 former smokers, and 36 current smokers. There was no difference between groups in regards to race or sex. There was no difference in the American Joint Committee on Cancer Clinical Stage Group between groups. The former smokers were significantly older when compared to never smokers and current smokers (66.5 ± 13.17 *vs* 57.4 ± 7.82 *vs* 63.7 ± 13.80, P = 0.011). Former smokers and current smokers had a higher recurrence rate compared to never smokers (30.8% and 20.8% compared to zero, P = 0.009). There was not a significant difference in recurrence between former smokers and current smokers. There was no difference in the mortality, non-response rate, or time to death

between the groups.

CONCLUSION
Our data contributes evidence that cigarette smoking status is associated with increased recurrence for patients with anal cancer.

Key Words: Anal cancer; Smoking; Recurrence; Nigro protocol; Chemoradiation; Retrospective review

Core Tip: This retrospective review examined the impact of smoking on anal cancer treatment for 95 patients. Smoking status was associated with a significantly higher rate of anal cancer recurrence after standard treatment. There was not a significant association between smoking status and anal cancer treatment non-response or mortality. Further study is needed to determine if smoking cessation would alter the course of anal cancer or if adjunct therapy would be beneficial in patients with anal cancer and a smoking history.

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INTRODUCTION

The incidence of anal cancer is increasing[1]. Several risk factors have been associated with anal cancer including human papilloma virus (HPV), HIV, age, immunosuppression, and smoking[1-3]. Although the association between anal cancer and smoking has been well-documented, the association between smoking status and recurrence is much less studied. A few prior studies have examined the impact of smoking status on anal cancer treatment, but these studies have been relatively small with the largest including 171 patients, while the other two included 64 and 68 patients[4-6]. Given smoking is a modifiable risk factor, studies examining its relationship with treatment success are important. This study aimed to contribute to the body of data examining treatments and outcomes for patients who smoke and have anal cancer.

MATERIALS AND METHODS

The study was conducted as a retrospective review of the cancer registry from a single health system. The registry was screened for patients with anal cancer between 2010 and 2020. All patients included in the registry were over the age of 18. The following characteristics were gathered from the database: Age; sex; cigarette smoking status; American Joint Committee on Cancer Clinical Stage Group; treatment pathway; response to therapy; recurrence; time to recurrence; mortality; time to death; and length of follow-up. Non-response was defined as persistent presence of disease despite completing standard chemoradiation. Recurrence was defined as the presence of disease after documentation that there was not any disease present. Unfortunately, HPV status and HIV status were not included in the database. Within the database, smoking status was divided into current smokers, never smokers, and former smokers. Smoking status was determined based on cigarette smoking alone. Current smokers were classified as any patient that reported cigarette smoking within 30 d of the time of diagnosis. Former smokers were classified as patients who had stopped smoking at least 30 d prior to diagnosis.

SPSSv25.0 software (IBM Corp., Armonk, NY, United States) was used for statistical analysis. Age and length of follow-up were analyzed between groups using single factor analysis of variance with Tukey post-hoc test. Patient race and sex were analyzed between groups using Fisher's exact test and Pearson's χ^2 test, respectively. *P* values were generated using an exact Mann-Whitney *U*-test to compare the mortality, non-response, recurrence, and time to recurrence between the current, former, and never smoker groups. In order to minimize type I error and given the small sample size, Bonferroni adjusted *z*-test was completed to compare the recurrence rate between groups. A subgroup analysis was completed to analyze time to death for the patients who did not respond using a single factor analysis of variance test.

RESULTS

A total of 95 patients were identified from the database. The patients were divided into three groups: Current smokers; former smokers; and never smokers. There was no significant difference in age, race, or sex between the groups (Table 1).

Table 1 Demographic data

Variable	Cigarette use			*P* value
	Never, *n* = 37	Former, *n* = 22	Current, *n* = 36	
Age in yr,				0.011
mean ± SD	63.70 ± 13.80	66.50 ± 13.17	57.40 ± 7.82	
Clinical stage group				0.066
1	5 (13.5)	4 (18.2)	8 (22.2)	
2	14 (37.8)	9 (40.9)	18 (50.0)	
3	14 (37.8)	9 (40.9)	8 (22.2)	
4	4 (10.8)	0	2 (5.6)	
Race				0.273
Black	2 (5.4)	0	4 (11.1)	
White	35 (94.6)	22 (100)	32 (88.9)	
Sex				0.078
Female	30 (81.1)	17 (77.3)	21 (58.3)	
Male	7 (18.9)	5 (22.7)	15 (41.7)	
Length of follow-up in d				0.759
mean ± SD	1195.10 ± 1135.96	1023.20 ± 855.35	1218.20 ± 986.20	

Data are *n* (%). SD: Standard deviation.

There was a difference in age between groups, with the former smokers being older than the smoker and never smoker groups (Table 1).

There was no significant difference in mortality or non-response between groups (Table 2). Former and current smokers did have a significantly higher recurrence rate compared to never smokers ($P = 0.009$). There was no difference in recurrence between the former and current smokers (Table 2).

Time to death was analyzed between the groups. On average, there was a shorter time to death in the current smoker arm, but this was not statistically significant (Table 3). The mortality rate between groups in the non-responder subset was also examined. Never smokers who did not respond to treatment were approximately twice as likely to die (43% *vs* 22%), but this did not achieve statistical significance (Table 3).

DISCUSSION

While three prior studies have examined the relationship between anal cancer treatment and smoking status, these studies have been small[4-6]. Our data contributes further evidence that smoking status is associated with a worse outcome and increased recurrence for patients with anal cancer. Additionally, it raises two interesting questions: (1) Should smokers and former smokers have more aggressive anal cancer treatment to reduce risk of recurrence?; and (2) Does smoking cessation result in an improvement in anal cancer outcomes? Lerman *et al*[4] raised the question of whether smokers would benefit from programmed cell death 1 inhibitors given the seemingly reduced efficacy of chemoradiation in smokers and a similar trend in non-small cell lung cancer. While our paper is limited in its evaluation, it does highlight the need for studies examining varying treatment options for smokers moving forward.

Interestingly, 14 of the never smoker patients did not respond to initial treatment. Of these patients, 43% died, with an average of 598 d after diagnosis (Table 3). This mortality rate was twice as high as the mortality rate for former and current smokers who did not respond. Although this did not achieve statistical significance due to the small numbers of this study, it is an interesting trend. One potential hypothesis is that never smokers who do not respond to initial therapy have a more aggressive tumor biology. Our data is not extensive enough to examine this further, but future research should examine this relationship. If confirmed, one could consider examining more aggressive treatment pathways for never smokers who do not respond to initial chemoradiation.

Unfortunately, the database used for this study did not include patient HPV status. This could be an important confounder that is not accounted for in this data. In similar cohorts of patients, 74%-88% of patients with anal cancer were HPV positive[1,3]. Although HPV is certainly linked to anal cancer, these same studies have shown that smoking status is an independent risk factor for anal cancer apart from HPV[1,3]. Additionally, the impact of HPV status on anal cancer outcome is not clear at this time as the two other largest studies examining anal cancer outcome and smoking status did not have HPV status collected for their cohorts either[4,5].

Table 2 Outcome data by group

Variable	Cigarette use			*P* value
	Never, *n* = 37	Former, *n* = 22	Current, *n* = 36	
Death	14 (37.8)	6 (27.3)	8 (22.2)	0.332
Non-response	14 (37.8)	9 (40.9)	14 (38.9)	0.973
Recurrence	0	4 (30.8)	5 (20.8)	0.009
Time to recurrence in d (median interquartile range)	NA	195.0 (159.0-351.0)	362.0 (214.5-1019.0)	0.413
Recurrence and non-response combined	14 (37.8)	13 (59.1)	18 (50.0)	0.264

NA: Not available.

Table 3 Mortality subgroup analysis

Feature	Cigarette use			*P* value
	Never	Former	Current	
Mortality* subgroup	*n* = 14	*n* = 6	*n* = 8	
Time to death in d, mean ± SD	598.30 ± 734.61	848.40 ± 756.83	393.80 ± 325.69	0.465
Non-responder subgroup	*n* = 14	*n* = 9	*n* = 14	
Deaths in non-responders subgroup, *n* (%)	6 (42.9)	2 (22.2)	3 (21.4)	0.285

*Death. SD: Standard deviation.

As noted before, this study is limited in its scope due to the retrospective nature and limitations of the collected data. A prospective study examining the impact of smoking cessation on anal cancer treatment would be valuable. Even without a prospective study, this study adds important data indicating an increased incidence of anal cancer recurrence in patients who smoke.

CONCLUSION

This paper highlighted the increased risk of anal cancer recurrence in patients who smoke. Although this study was small and limited in its scope, compared to current literature it is the second largest cohort of patients examining anal cancer, smoking, and recurrence. Further research is needed to examine the impact of smoking cessation on anal cancer treatment outcome and if adjuncts to standard therapy would be beneficial in patients who smoke.

ARTICLE HIGHLIGHTS

Research background

Despite the occurrence of approximately 50000 new cases of anal cancer per year and the clear link with smoking, very few studies have examined the relationship between smoking status and treatment outcome. It has already been shown that there is a link between anal cancer and smoking. This paper goes further and showed that there was an increased risk of recurrence in patients who smoke and have a history of smoking. This serves as a foundation for future research to examine modifications to the current treatment approach for patients with anal cancer.

Research motivation

Investigating the relationship between cigarette smoking status and anal cancer treatment outcome.

Research objectives

The main objective of this study was to examine the relationship between smoking status and outcomes for patients with anal cancer.

Research methods

A total of 95 patients were included in this data, making it the second largest study to examine the impact of smoking on anal cancer treatment outcomes. The patients were similar between the groups (never smokers, former smokers, and current smokers) in regards to important factors such as clinical stage group, race, and sex. Former and current smokers had a higher recurrence rate compared to never smokers. There was no difference in the mortality, non-response rate, or time to death between the groups. Unfortunately, data did not include human papilloma virus status, which would be an important area to include for future research.

Research results

There was an increased risk of anal cancer recurrence in patients who currently smoke and have a history of smoking.

Research conclusions

This study was the second largest study examining the relationship between treatment outcome and smoking status in patients with anal cancer. Although this data was limited in its scope, it contributed further to the limited body of evidence that smoking increases risk of recurrence of anal cancer.

Research perspectives

Future research should examine the impact of smoking cessation on treatment outcomes for patients with anal cancer as well as the role of adjuncts to standard chemoradiation in the treatment of anal cancer.

FOOTNOTES

Author contributions: McMahon KR designed and performed the research and wrote the paper; Gemma N helped write and revise the report; Dibello J assisted with data curation and editing of the report; Clapp M assisted with data curation and editing the report; Sanchez-Montejo P assisted with data analysis and editing the report; Laipply E designed the research and supervised the report.

Institutional review board statement: The study was reviewed and approved by the Summa Health System Institutional Review Board (Approval No. 21176).

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Country/Territory of origin: United States

ORCID number: Kevin R McMahon 0000-0003-3881-0175.

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SYSTEMATIC REVIEWS

Cancer screening and management in the transgender population: Review of literature and special considerations for gender affirmation surgery

Juliet C Panichella, Sthefano Araya, Siddhartha Nannapaneni, Samuel G Robinson, Susan You, Sarah M Gubara, Maria T Gebreyesus, Theresa Webster, Sameer A Patel, Alireza Hamidian Jahromi

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Juliet C Panichella, Samuel G Robinson, Susan You, Sarah M Gubara, Maria T Gebreyesus, Lewis Katz School of Medicine, Temple University, Philadelphia, PA 19140, United States

Sthefano Araya, Siddhartha Nannapaneni, Sameer A Patel, Division of Plastic and Reconstructive Surgery, Fox Chase Cancer Center, Philadelphia, PA 19111, United States

Theresa Webster, Department of Plastic Surgery, Temple University, Philadelphia, PA 18045, United States

Alireza Hamidian Jahromi, Division of Plastic and Reconstructive Surgery, Temple University Hospitals, Philadelphia, PA 19140, United States

Corresponding author: Alireza Hamidian Jahromi, MD, MRCS, Division of Plastic and Reconstructive Surgery, Temple University Hospitals, 3401 Broad Street, Philadelphia, PA 19140, United States. alirezahamidian@yahoo.com

Abstract

BACKGROUND

Literature focused on cancer screening and management is lacking in the transgender population.

AIM

To action to increase contributions to the scientific literature that drives the creation of cancer screening and management protocols for transgender and gender nonconforming (TGNC) patients.

METHODS

We performed a systematic search of PubMed on January 5th, 2022, with the following terms: "TGNC", OR "transgender", OR "gender non-conforming", OR "gender nonbinary" AND "cancer screening", AND "breast cancer", AND "cervical cancer", AND "uterine cancer", AND "ovarian cancer", AND "prostate cancer", AND "testicular cancer", AND "surveillance", AND "follow-up", AND "management". 70 unique publications were used. The findings are discussed under "Screening" and "Management" categories.

RESULTS

Screening: Current cancer screening recommendations default to cis-gender protocols. However, long-term gender-affirming hormone therapy and loss to follow-up from the gender-specific specialties contribute to a higher risk for cancer development and possible delayed detection. The only known screening guidelines made specifically for this population are from the American College of Radiology for breast cancer. Management: Prior to undergoing Gender Affirmation Surgery (GAS), discussion should address cancer screening and management in the organs remaining in situ. Cancer treatment in this population requires consideration for chemotherapy, radiation, surgery and/or reconstruction. Modification of hormone therapy is decided on a case-by-case basis. The use of prophylactic *vs* aesthetic techniques in surgery is still debated.

CONCLUSION

When assessing transgender individuals for GAS, a discussion on the future oncologic risk of the sex-specific organs remaining in situ is essential. Cancer management in this population requires a multidisciplinary approach while the care should be highly individualized with considerations to social, medical, surgical and gender affirming surgery related specifications. Special considerations have to be made during planning for GAS as surgery will alter the anatomy and may render the organ difficult to sample for screening purposes. A discussion with the patient regarding the oncologic risk of remaining organs is imperative prior to GAS. Other special considerations to screening such as the conscious or unconscious will to unassociated with their remaining organs is also a key point to address. We currently lack high quality studies pertinent to the cancer topic in the gender affirmation literature. Further research is required to ensure more comprehensive and individualized care for this population.

Key Words: Gender affirmation surgery; Gender affirming surgery; Screening; Management; Transgender; Gender diverse

Core Tip: Currently, a comprehensive guideline for cancer screening in the transgender and gender diverse (TGGD) population is lacking. Caring for the TGGD population undergoing Gender Affirmation Surgery is highly individualized and requires consideration of factors such as age at which individuals commenced hormonal therapy and the stage of transition. Once diagnosed with cancer, TGGD patients should receive care at institutions capable of providing a multi-disciplinary approach. This collective approach will ensure record upkeep and help delay any unnecessary delays in care.

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INTRODUCTION

The transgender and gender diverse (TGGD) population in the United States is estimated to be around 1.4 million, constituting 0.6% of the United States adult population[1]. There exists no census data to back this estimate and may be higher in the younger population. It is well known that cancer screening has led to a decrease in cancer mortality. Many organizations including American Cancer Society (ACS), United States Preventive Services Task Force (USPSTF) have clear recommendations for the early detection of cancer in cis-gender individuals. However, the TGGD population currently has no cancer screening recommendations specific to the TGGD population. The World Professional Association for Transgender Health, a non-profit, interdisciplinary professional and educational organization devoted to transgender health, states that due to a lack of prospective studies, there is not enough evidence for the recommendation of the appropriate type and frequency of screening in this population[2].

In addition to screening, no studies have commented on gender affirming surgery (GAS) and its impact on the screening, management, and surveillance of cancer in the TGGD population. Special considerations must be made during planning for GAS as surgery will alter the anatomy and may render the organ difficult to sample for screening purposes *i.e.*, prostate evaluation following the penile inversion vaginoplasty in the transgender woman. A discussion with the patient regarding the oncologic risk of remaining organs is imperative prior to GAS.

Of note, in this article, the distinction between sex and gender is made based on the former referring objectively to biology and the latter subjectively being psychosocially constructed. Overall, this article aims to review the current guidelines and practice patterns with regard to cancer screening and management in each sex-specific organ for the TGGD population.

MATERIALS AND METHODS

A systematic search of PubMed on January 5th, 2022, with the following terms: "TGNC", OR "transgender", OR "gender non-conforming", OR "gender nonbinary" AND "cancer screening", AND "breast cancer", AND "cervical cancer", AND "uterine cancer", AND "ovarian cancer", AND "prostate cancer", AND "testicular cancer", AND "surveillance", AND "follow-up", AND "management". After eliminating review articles, duplicates, abstracts, articles not relevant to the section topic or opinion pieces a total of 70 studies with original data were obtained (Figure 1). Articles relevant to the section topic, including the search terms were included in this systematic review. Search parameters were performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Two independent reviewers Araya S and Nannapaneni S carried out independent abstract revisions on January 11th, 2022, using systematic review software "Rayyan"[3] registered in Cambridge Massachusetts.

RESULTS

Breast

The PubMed Database was queried from April 1968 to January 2022 using the search text of "(gender nonbinary) OR (transgender and gender non conforming) OR (transsexual) AND (breast cancer)". This search produced 190 unique articles. Of these articles, 60 were assessed for eligibility and sub-classified based on the primary content of the paper as either screening or management relating to the breast. The term "transsexual" is outdated. However, as our search would span to the remote past, we used this term to be able to identify older publications.

Barriers to care

In addition to the physical limitations that GAS can impose on cancer screening, it is equally important to acknowledge the psychological health of each individual patient and the impact of gender dysphoria on their attitude towards the cancer screening process. The lack of protocols and education surrounding TGGD patients provided to healthcare workers has led to an environment where both providers and patients are uncomfortable with the quality healthcare currently being provided[4-10]. Finally, GAS adds to the technical complexity of oncologic screening protocols.

In different retrospective population studies, authors reported that while 92% of studied transgender men have retained their cervixes, they were 60% less likely to undergo cervical cancer screening, 70% less likely to have breast cancer screening, and 50% less likely to have colorectal cancer screening compared to cis-gender patients[9,11,12]. Of note, it is uncommon to remove the prostate during vaginoplasty in transgender women and these patients are also significantly less likely to receive prostate cancer screenings compared to their cis-gender counterparts[13].

While some of these discrepancies can be attributed to differences in demographics as TGGD patients tend to be of a lower socioeconomic status, there are also hurdles these patients face within the healthcare system - including history of prior trauma, provider knowledge deficits, fear of mistreatment or mis-gendering, and lack of appropriate restrooms, gender affirming spaces or educational material[4-9]. There are also disparities of gender affirmation care, gender friendly facilities and services between different parts of the country.

As an example, the ACS recommendation for mammograms for women would miss screening of trans men or nonbinary people for whom the "chest" screening is relevant. Additionally, the lack of gender friendly language may create an additional barrier to care. Some TGGD individuals may want to mentally detach themselves from gender attributed organs *i.e.*, prostate in transgender women or breast in transgender men and attributed screening *i.e.*, a mammogram in the case of a transgender man as this may exacerbate their gender dysphoria. The mention of organs such as "breast" instead of "chest" or "vagina" instead of "current canal" can further promote gender dysphoria in TGGD individuals, and as a result, they are less likely to receive such life-saving screening[4].

Seventy percent of TGGD patients have reported some form of distrust with the healthcare system, and 33% of patients in this population have had negative experiences with healthcare providers that have ranged from incompetent providers and being refused care to harassment and assault[8,9,12]. During the time of the coronavirus disease 2019 pandemic, there has been an increase in anxiety, depression, and suicidal ideation among TGGD patients so providers should be mindful of the mental stress that these patients undergo in addition to the fear and mistrust they have experienced within the healthcare system[14]. Not only do providers need to be explicit in their welcoming of TGGD patients, but they need to invoke flexible methods of meeting the patients' needs, such as patient-collected HPV swabs, interviewing the patient prior to disrobing, creating a gender friendly environment *i.e.*, introducing themselves with their pronouns and the use of gender-inclusive language[4]. Providers also need to remain up to date on TGGD cancer screening recommendations as a study of gynecological providers found that only 35% felt comfortable providing gynecologic care to this community and even fewer (29%) felt equipped to do so[10]. The utilization of health navigators offers an additional form of support and knowledge for both patients and providers in accomplishing the best care of the patient[15].

Breast

Breast cancer is the most common form of cancer in cis-gender women and the second most common cause of cancer mortality in cis-gender women in the United States[16]. However, the reported lifetime risk for TGGD individuals is not reported due to insufficient data and research. Every year, more case studies are reported of TGGD individuals developing breast cancer. Studies have shown increased rates of breast cancer in TGGD women compared with cis-gender males, as well as a decreased risk of breast cancer in TGGD men compared to cis-gender females. For transgender men who have undergone chest surgery to remove the breasts, the decreased risk of breast cancer is an expected finding

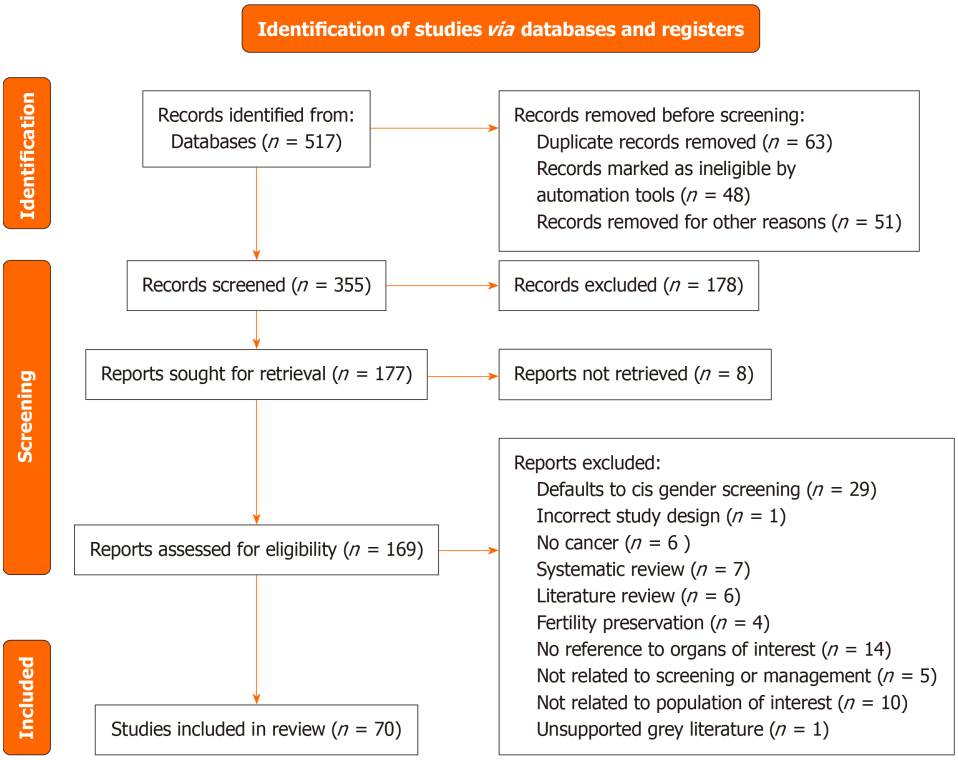

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Figure 1 The preferred reporting items for systematic reviews and meta-analyses flowchart for overall cancer screening and management in the gender affirming surgery population.

and consistent with risk reducing mastectomy in the cis-gender female population[17]. However, there is a lack of data and recommendations on breast cancer screening and management of TGGD patients. This is compounded by the inherent risk of discrimination and poor access/barriers to healthcare in the TGGD population, leading to a high rate of disease progression before diagnosis[18,19]. This systematic review aims to elucidate the screening and management of breast cancer in TGGD individuals with a goal of improved care and treatment.

Screening

Of the 89 records screened, 30 records were sought for retrieval pertaining to screening for breast cancer in TGGD patients. The majority of these articles (*n* = 29) deferred management to cis-gender guidelines for TGGD patients or called for more studies on TGGD-specific screening recommendations (Figure 2A). Nevertheless, our review identified and included one article that was a comprehensively covered, evidence-based, breast cancer screening guideline for TGGD individuals provided by the American College of Radiology Appropriateness Criteria in 2021 (Figure 2A)[20]. These guidelines cover eight different variants of screening based on classification of gender affirming surgery, age, duration of exogenous hormone use, and risk category. Recommendations are graded for each variant by appropriateness categories including "Usually appropriate", "May be appropriate", and "Usually not appropriate". Each modality is also considered in relation to the amount of radiation involved. Screening modalities include digital breast tomosynthesis (DBT) screening, mammography screening, magnetic resonance imaging (MRI) breast with and without IV contrast, and ultrasound of breast. Overall, the higher the age, longer the length of use of hormones, and higher the risk category, the more appropriate the use of DBT and MRI becomes.

Management

Transgender women can undergo a variety of breast augmentation surgery procedures to create a feminine appearing chest. Included in this population are non binary individuals who may also undergo breast augmentation procedures. Breasts can be created through a variety of methods, including hormone therapy, fat grafting, saline implants or silicone implants, or autologous reconstruction. Chest masculinization, colloquially referred to as "top surgery", can be performed to create a more masculine appearing chest. Breast tissue is either reduced or completely removed *via* liposuction, mastopexy, or mastectomy to create a flat chest, while the nipples can be completely removed and/or resized and repositioned. The authors believe and practice with the gender spectrum concept and as such acknowledge the desired chest to be a spectrum.

Breast cancer in the cis-gender individuals is managed surgically with breast conserving surgery (lumpectomy and radiation), and/or mastectomy. Treatment may also include adjuvant or neoadjuvant chemotherapy and/or radiation pending nodal status along with hormonal therapy with anti-estrogen agents pending hormone receptor status. Currently, breast cancer in the TGGD individual is managed similarly. However, in TGGD patients, the timing of cancer presentation in relation to gender affirming surgery, as well as timing in relation to the use of hormone therapy are

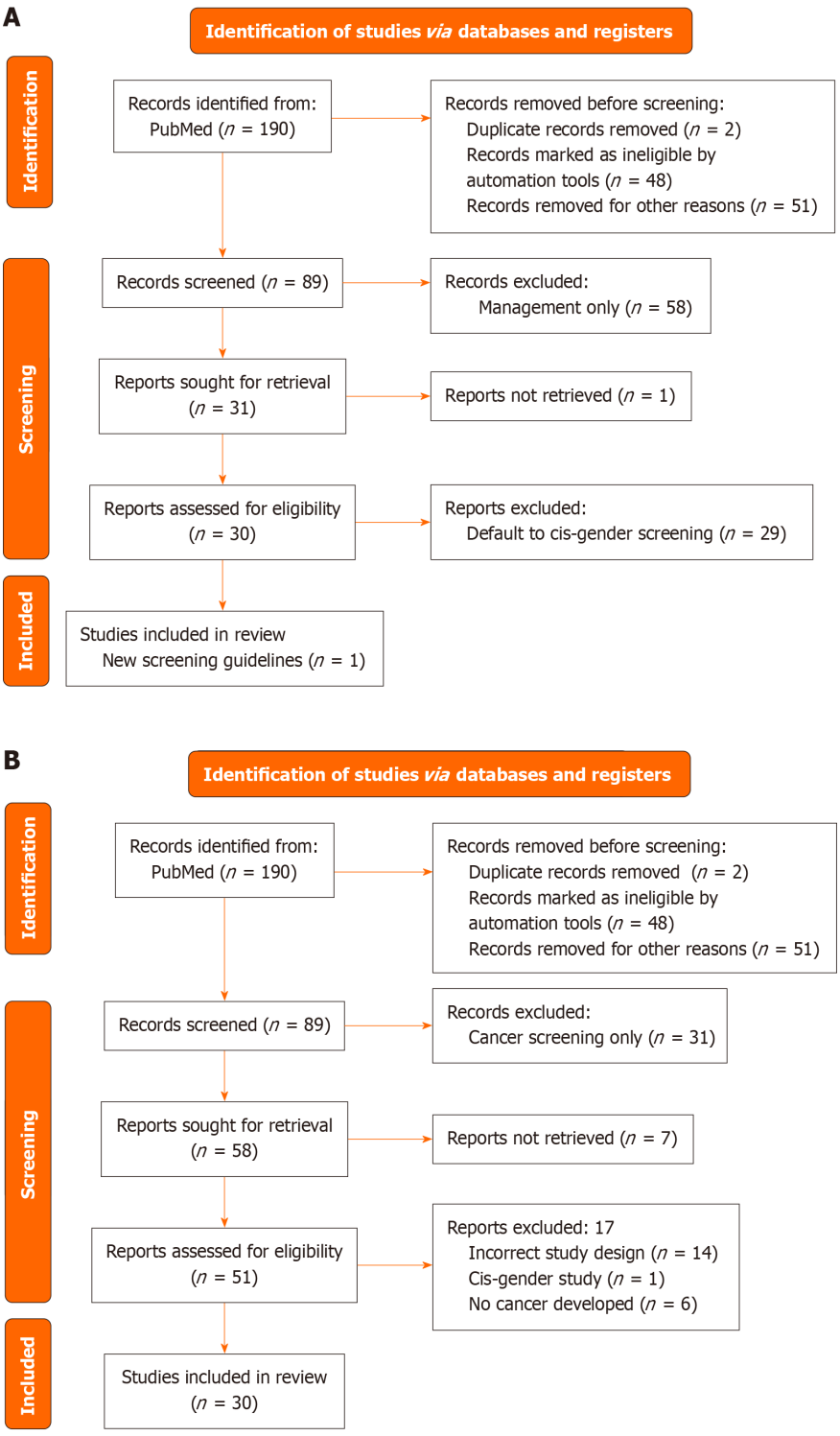

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Figure 2 The preferred reporting items for systematic reviews and meta-analyses charts for the breast screening and management. A: The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for articles about breast cancer screening; B: PRISMA flowchart for breast cancer management.

additional variables that will affect management.

Of the 89 records screened, 58 of them were sought for retrieval related specifically to management of breast cancer in TGGD patients. Of that 58, there were 30 case reports of breast cancer in TGGD patients (Figure 2B).

Chest Feminization Gender Affirming Surgery

There was a total of 25 male to female (MtF) gender affirming surgery cases among 18 case studies. Each group was further categorized according to hormonal status, gender affirming surgery, and the timing of detection (immediate or delayed) (Figure 3). Immediate detection describes patients whose breast cancer was discovered at the time of gender-

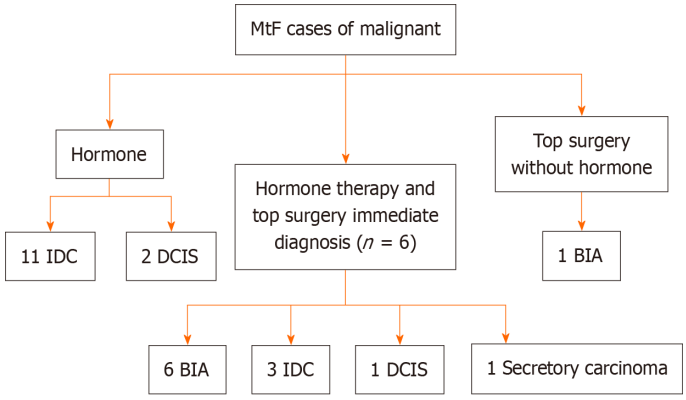

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Figure 3 Study design for male to female gender affirming surgery patients. MtF: Male to female; IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; BIA: Breast implant associated.

affirming breast augmentation. Delayed detection describes cases of breast cancer that were detected after breast augmentation. Patients that did not undergo surgery or hormone therapy were excluded as we were largely interested in understanding how these factors influenced breast cancer detection and management. Patients who were not diagnosed with breast cancer were excluded (Figure 2B).

Cancer Detection In Patients With Hormonal Therapy Only

Eleven papers identified 13 patients who were on estrogen hormone therapy regimens before gender affirming breast surgery. Of the 13 patient studies, two were diagnosed with ductal carcinoma in situ (DCIS) and 11 patients were diagnosed with Infiltrating Ductal Carcinoma (IDC). The average age of cancer diagnosis was 53.8 years old. The average time on hormone therapy prior to the surgery was 16.5 years. All patients mentioned were diagnosed with cancer.

Of the two patients who were diagnosed with DCIS, both had cancer that are Estrogen receptor (ER) positive. One patient demonstrated Progesterone receptor (PR) positive DCIS and hormone treatment was discontinued in the other patient who was PR negative. Additionally, the latter patient was further treated with lumpectomy and radiation with sentinel lymph node sampling, adjuvant chemotherapy, and aromatase inhibitor without any reported recurrence[21]. The patient with ER+/PR+ cancer reported family history of ovarian cancer and a mutation in Chek2 p.I157T, which confers a 1.4 increased risk of breast cancer development. Despite the higher risks, hormone therapy was not discontinued, and the patient was treated with breast conservation surgery and radiation without anti-estrogen therapy according to the patient's wishes. No follow-up recurrence was reported[22]. The difference in the treatment can be attributed to patient desires. Despite being aware of the higher risk, the patient opted to continue hormonal therapy and forgo anti-estrogen therapy.

In the group of 11 patients who were diagnosed with IDC, there was a variety of hormonal receptor status, treatments, and outcomes. Six patients had ER+/PR+ cancers. Of these six, two were positive for BRCA2 mutations. Both patients elected to discontinue hormone therapy[23,24]. The first patient declined tamoxifen and was just surgically treated with a simple unilateral mastectomy of the right side with sentinel lymph node biopsy. Local recurrence occurred 30 mo later and treatment with radiation therapy and adjuvant chemotherapy with aromatase inhibitors (epirubicin plus cyclophosphamide w/paclitaxel)[23]. The other patient was treated with bilateral mastectomy and sentinel lymph node dissection, neoadjuvant tamoxifen and adjuvant radiation (patient declined chemotherapy). No recurrence was reported[24]. This brings up the discussion on what treatment options should be for patients who are positive for BRCA2 mutations. Additionally, it is difficult to know whether ER positivity in these two patients is due to hormone therapy or the mutation itself[24]. This may require more research to determine the effect of BRCA2 mutations on ER+ cancer in the presence of gender affirming hormone (GAH) therapy.

The other four ER+ IDC patients were treated with tamoxifen. One of these patients did not stop hormone therapy and had good outcomes from treatment while two patients who did stop hormone therapy treatment did die from complications of metastatic breast cancer, 22 mo and 6.5 years after their diagnoses[25,26]. This further highlights the necessity to determine what the real impact of GAH therapy in on cancer. Further research is required to mitigate risk of gender-affirming care hormone therapy continuation.

Three patients were diagnosed with triple negative IDC, each of whom were taking hormone therapy for more than 10 years. One patient was only treated with tamoxifen after local wide excision and axillary clearance and did not discontinue their hormone therapy, Premarin. This patient reached remission and remained cancer free after 1 year of follow up[25]. The other two patients did discontinue hormone therapy treatment. Both of these patients were non-surgically treated with neoadjuvant chemotherapy and adjuvant radiation[27,28]. The first patient had no family history of breast cancer and genetic testing found no clinically significant mutations that would increase her risk. However, it should be noted that this patient had significant comorbidities including HIV that was well managed with medication, and depression that was managed through counseling. Additionally, though the patient was ER (-), her healthcare team decided to discontinue use of estrogen therapy to prevent the development of an ER+ tumor subset/second tumor. In addition to management of her breast cancer the patient attended counseling for management of psychological distress

attributed to the cessation of estrogen[27].

A second patient with comorbid severe depression on antipsychotic medications and possible secondary hyperprolactinemia attributed to the medications was managed with cessation of GAHs. The patient's cancer progressed and ultimately expired by intentional drug overdose[28]. Concerns of a patient's mental status due to aggravation of gender dysphoria and loss of feminine characteristics when halting hormone therapy and even creation of suicidal ideation *vs* the risk/benefit of hormone therapy on prolactin and cancer incidence is a debated issue in the current literature[28]. Authors describe prolactin screening for patients on long term estrogen given the possible tumor promoter actions in breast and prostate cancer[28].

Cancer Detection After Chest Feminization

Patients taking GAHs: This group received treatment with hormone therapy and underwent gender affirming breast augmentation surgery with implants prior to cancer diagnosis. There were 11 patients[6], who were diagnosed with Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), three who were diagnosed with IDC, one who was diagnosed with DCIS, and one patient who presented with a triple negative secretory carcinoma caused by a *ETV6-NTRK3* gene fusion mutation though no treatment was discussed[29]. The average age of cancer diagnosis was 45.3 years old. The average time on hormone therapy was 14.2 years.

The finding of six TGGD patients diagnosed with BIA-ALCL has implications on health care. For surgical treatment, all were treated with implant removal, capsulectomy, and tumor resection as per treatment in cis-gender women with ALCL [30-32]. This treatment has been shown to improve disease-free survival[32]. Complete surgical resection with *en-bloc* removal of the disease, implant, and capsule provides the best survival outcomes. However, for patients with extensive disease and regional lymph node involvement, adjuvant chemotherapy and/or radiation may be recommended[30].

According to the most recent National Comprehensive Cancer Network (NCCN) guidelines in the United States, adjuvant radiation therapy is indicated for patients with local residual disease with or without regional lymph node involvement or unresectable disease with chest wall invasion. Systemic chemotherapy is indicated for patients with Stage II–IV disease[32]. All six patients received textured implants, a possible risk factor for the formation of BIA-ALCL[33].

Three patients were diagnosed with IDC. One of the patients was advised to discontinue hormone therapy, however, decided to continue it against medical advice. No length of follow up or recurrence was reported[34]. However, the authors present an interesting debate as to what the acceptable balance of risk *vs* benefit is for cessation of hormone therapy in this group of patients given the often competing oncologic *vs* gender affirming interests[34].

Patients not taking GAHs: One paper identified a TGGD patient who underwent gender affirming breast augmentation surgery without prior hormone therapy treatment[32]. This patient was diagnosed with BIA-ALCL and subsequently treated with bilateral implant removal and capsulectomy of the affected side. The patient did not receive any radiation or chemotherapy and was tumor-free 10 mo post-operatively[32].

Chest Masculinizing Gender Affirming Surgery

There was a total of 16 female to male gender affirming surgery patients among 12 case studies. Each group was further categorized according to hormonal status, gender affirming surgery, and the timing of detection (immediate or delayed) (Figure 4). Immediate detection describes patients whose breast cancer was discovered at the time of gender-affirming top surgery. Delayed detection describes cases of breast cancer that were detected after top surgery. Patients that did not undergo surgery or hormone therapy were excluded as we were largely interested in understanding how these factors influenced breast cancer detection and management. Patients who were not diagnosed with breast cancer were excluded (Figure 2B).

Cancer Detection Prior To Chest Masculinization

Four patients (out of 12 patients) among three papers were identified with intramuscular testosterone usage and development of breast cancer prior to top surgery (mastectomies)[26,35,36]. All four patients developed an IDC. There was a mix of hormone receptor positivity with no specific trend. The average time on intramuscular testosterone therapy was 4.7 years. The average age at diagnosis was 46.3 years old. Four patients among two papers were excluded due to no hormone therapy used[21,26].

One patient with ER+/PR+/HER2+/AR+ IDC was treated with bilateral mastectomies with right sentinel lymph node biopsy, nipple-areolar grafting, neoadjuvant chemotherapy, and continuation of testosterone therapy survived an unknown amount of time. A second patient diagnosed with ER+/PR-/HER2+ IDC was treated with unilateral mastectomy and adjuvant chemotherapy. Management with testosterone therapy was unknown. The patient expired within two years. A third patient with ER+/PR+ IDC was treated with lumpectomy, followed by bilateral nipple-sparing mastectomies 1 year later and unknown management of testosterone therapy after diagnosis was in remission at least 10 years. The fourth patient with ER-/PR+ IDC bilateral managed with nipple sparing mastectomy, adjuvant and neoadjuvant chemotherapy with permanent discontinuation of hormone therapy was in remission at least 5 years. Unfortunately, the sparse number of cases studied and incomplete patient history and follow up in these patients do not provide a good platform to draw conclusions for hormone continuation, surgical management, or survival.

One of the patients developed a clinically interesting finding of an androgen receptor (AR) positive IDC[37,38]. The authors of this paper emphasized the importance of testing for AR sensitivity in TGGD patients as some of the patients may be taking testosterone and stopping the hormone may impact their gender dysphoria. However, continuing GAH therapy could lead to progression or recurrence of the cancer after treatment given the cancer's responsiveness to the AR sensitivity.

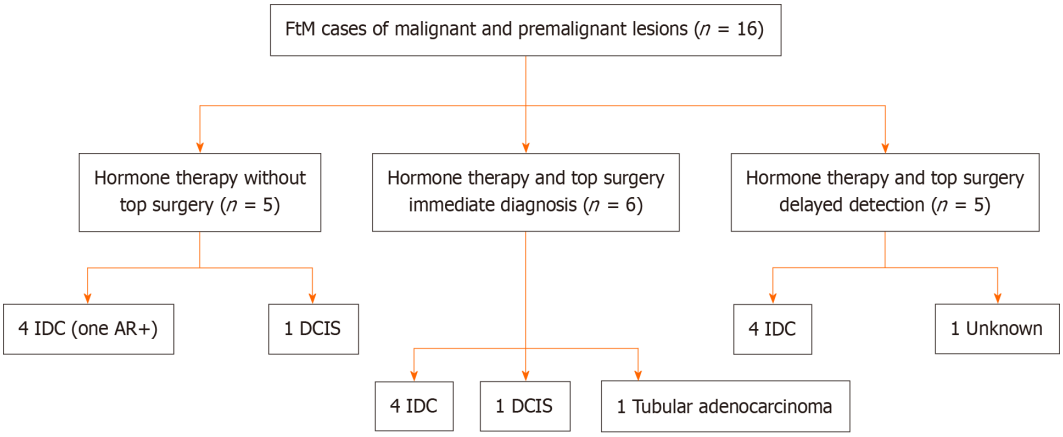

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Figure 4 Study design for female to male gender affirming surgery patients. FtM: Female to male; IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; AR: Androgen receptor.

One patient developed DCIS, a premalignant lesion, in the setting of testosterone therapy. This is an interesting finding as even a premalignant lesion is a risk later down the line for these patients and begs the question of needing oncologic mastectomy to completely mitigate the risk. It is important to mention that the DCIS in the cis gender individual, not on androgen therapy, can undergo a risk reduction with hormone blockers and wide local excision and may not particularly necessitate a mastectomy. Had this pathology not been caught in the pre-operative setting, this patient could have been found to have a cancer or DCIS later during the top surgery or even in rare occasions in the post top surgery setting *i.e.*, in case the residual breast tissue will keep the burden of DCIS pathology. Therefore, this situation emphasizes the importance reevaluating GAH dosing or discussing discontinuing the hormone altogether.

Cancer Detection After Chest Masculinization

Immediate detection (surgical pathology): Five patients (out of 9 total patients) were found to have cancer based on surgical specimens sent for histologic evaluation during their top surgery. Four of these patients had invasive ductal carcinoma, one developed tubular adenocarcinoma[21,38,39]. In addition, one patient's pathology revealed a high grade DCIS[40]. The mean time on intramuscular testosterone therapy was 11.2 years. The average age at diagnosis was 45.4 years old. There were no patients that were found to have cancer during top surgery that did not take hormone therapy beforehand.

One patient with ER+/PR-/HER2- IDC was treated with bilateral mastectomies along with axillary lymph node dissection and chemotherapy. Later that patient presented with recurrence and underwent re-excision, radiotherapy, and tamoxifen treatment with unknown management of testosterone therapy after diagnosis with remission. Another patient with ER+/PR-/HER2+ IDC was treated after bilateral mastectomy with sentinel lymph node dissection plus chemotherapy. After a temporary discontinuation of testosterone therapy, the patient went into full remission. A third patient who was ER+/PR+/HER2+ IDC was treated with bilateral mastectomy with axillary lymph node dissection plus chemotherapy. After temporary discontinuation of testosterone, the patient had unknown survival. A fourth patient with ER+/PR+/HER2- IDC was treated after partial mastectomy breast reduction with full left mastectomy with sentinel node sampling with anastrozole plus radiation. After permanent discontinuation of testosterone, the patient had unknown survival. Finally, the last patient with ER+/PR+/HER2- tubular adenocarcinoma was treated with mastectomy and had a negative sentinel node biopsy. They did not discontinue testosterone, and received no further treatment, but had an unknown survival.

Overall, this section emphasizes the potential impact of having pathology sent for specimens at the time of surgery as earlier intervention on these patients could only improve the survival. All of these patients opted for full mastectomy (if not already done), whether unilateral or bilateral, for treatment of the cancer. Unfortunately, we are unable to draw clear conclusions from this subgroup for guidance on hormone discontinuation and survival outcome. However, one retrospective review comments on the increased risk of premalignant lesions and cancer found in surgical specimens of 193 bilateral mastectomies for TGGD patients both with and without hormones and reported an incidence of 8.8% of atypical lesions requiring further investigation[41]. Thus, even if no malignancy is anticipated in these patients, they would benefit from sending surgical specimens for pathologic evaluation.

Delayed detection (no surgical pathology): Four patients among five papers were found to have cancer based on screening post mastectomy. The mean amount of time post mastectomy for cancer diagnosis was 10 years. Four patients developed invasive ductal carcinoma, one patient's diagnosis was unknown[42-44]. The average time on intramuscular testosterone therapy was 7.7 years. The mean time after the first breast surgery was 10 years. The average age at diagnosis was 46.2 years old.

One patient with ER+/PR+/HER2 equivocal metastatic IDC discovered 20 years after bilateral mastectomy with free nipple grafts with unknown testosterone hormone management post diagnosis was treated with letrozole and had unknown survival. A second patient with ER+/PR+/AR+/HER2- IDC discovered 12 years post mastectomy, was treated

with breast partial resection, sentinel lymph node dissection, radiation therapy and aromatase inhibitors (patient refused tamoxifen due to feminization effects) with unknown testosterone hormone management post diagnosis and had unknown survival. A third patient who was diagnosed with triple negative IDC discovered seven years after bilateral mastectomy was treated with lumpectomy and adjuvant chemotherapy. This patient had unknown testosterone hormone management and had survived at least two years after treatment. A fourth patient with ER-/PR- metastatic IDC discovered one year after bilateral subcutaneous nipple sparing mastectomy was treated with neoadjuvant chemotherapy and radical mastectomy with axillary dissection. This patient had unknown testosterone hormone management post diagnosis and had unknown survival.

This subgroup of patients poses an interesting discussion of reduced risk of cancer from previous mastectomy, yet development of cancer in residual breast tissue shows such risk reduction not to be absolute. This would be due to the incomplete removal of breast tissue and pre-pectoral fascia in those that go for gender affirmation mastectomies *vs* oncologic mastectomies. The question as to whether we should offer a completion of (full oncologic) mastectomies (removing the pectoral fascia and the nipples) for such GAS patients remains uncertain. However, since the nature of these patients is higher loss to follow up and noncompliance with traditional screening, in addition to taking hormones, this population could be at higher risk than others for surreptitious development of cancer. Thus, they might benefit from a prophylactic oncologic mastectomy rather than a gender affirmation (subcutaneous) mastectomy. Clearly, this needs to be weighed against the cosmetic benefits of a subcutaneous mastectomy with nipple-areolar preservation and the quality-of-life implications that it affords.

BRCA

Of the 30 case studies, four patients were identified who were positive for BRCA2[23,24,33]. These four patients were transgender women. In cis-gender females with BRCA 1 or 2 mutation the lifetime risk of developing breast cancer is 55%-72%, while the lifetime risk in cis-females in 13%. In cis-gender men with a BRCA2 gene mutation, the lifetime risk of breast cancer is approximately 7 to 8 percent, while the lifetime risk of male breast cancer in the general population is approximately 0.1 percent[45,46].

In one case report, the patient, transgender woman, underwent bilateral skin-sparing mastectomy after confirming they were BRCA2 positive. A second patient, transgender woman, developed IDC two years after starting hormone therapy. She had bilateral mastectomies with immediate expander reconstruction and right sentinel lymph node sampling as well as adjuvant radiation therapy and then subsequently tested positive for BRCA2. A third patient, transgender woman, developed IDC after seven years on hormone therapy and underwent a right simple mastectomy with sentinel lymph node biopsy. There was recurrence 30 mo post-mastectomy, so radiation therapy and adjuvant chemotherapy were given as treatment. A fourth patient was identified as BRCA2 positive but had not developed cancer yet.

One of the most important points to be made about this subgroup analysis is that all six patients discontinued gender-affirming hormone therapy upon diagnosis with BRCA mutations. This seems to be the current standard of practice for management of these patients yet many patients choose not to discontinue hormone therapy. In fact, our review came across a few arguments against cessation, namely the history of treating advanced breast cancer with low dose estrogens and the deleterious effects of cessation on the mental well-being of TGGD patients[24,26,33]. More research is required to determine if there is a true therapeutic benefit to cessation of GAHs. Our systematic review also identified recommendations such as offering TGGD women who are BRCA1/2 positive risk-reducing mastectomies prior to breast augmentation rather than traditional aesthetic chest. Additionally, from oncology point of view TGGD men should be offered risk reducing mastectomies (gender affirmation subcutaneous mastectomies) over aesthetic chest surgeries[47]. It should be noted that there can be issues of coverage for certain procedures by insurance when the sex indicated on the patient's chart does not align with the sex-intended procedure especially if the insurance policies do not cover the gender affirmation as a separate group of procedure entities[47].

Additionally, this brings up an interesting discussion of whether we should routinely test these patients for BRCA before undergoing surgical intervention, or even prior to hormone initiation. This patient population would inherently benefit from more prophylactic interventions given the higher loss to follow-up and screening. Recommendations for the surgical management of the BRCA+ TGGD patients follow similar guidelines to the cis-gender individual for risk-reducing bilateral mastectomies over conservative, primarily aesthetic breast reductions. Overall, more studies need to be done to elucidate and strengthen further recommendations with regard to BRCA management in TGGD.

BIA-ALCL

Our search yielded seven cases of breast implant associated-anaplastic large cell lymphoma in transgender women[32,48]. There is a known increased risk of developing BIA-ALCL in cis-gender women with textured implants[32]. Thus, this risk is conferred in TGGD females as well. Loss of follow up and willing to seek medical attention may be further exacerbated by lack of provider knowledge on gender friendly language ultimately leading to delayed recognition and diagnosis[32]. Avoidance of gender specific language such as "breast" instead of "chest" as reference for anatomical parts may assist with patient willingness for follow-up and screening.

One patient underwent unilateral mastectomy (implant previously removed) with resection of pectoral muscle, and axillary node dissection and received chemotherapy. The second one underwent bilateral *en-bloc* resection of capsule and implant. The third one underwent *en-bloc* resection of implant, capsule, and mass (resection included part of pectoral muscle) plus chemotherapy. The fourth one underwent bilateral *en-bloc* resection of capsule and implant plus sentinel lymph node biopsy, excision of active lymph node and chemotherapy. The fifth patient underwent *en-bloc* resection of the capsule and implant. The sixth one underwent bilateral *en-bloc* resection of capsule and implant plus sentinel lymph node biopsy, along with chemotherapy and adjuvant radiation therapy. The seventh patient underwent bilateral *en-bloc*

resection of capsule, implant and tumor plus chemotherapy. The average time to diagnosis was 13.4 years, which is slightly more delayed yet comparable to cis-gender timeline of 9.75 years[49].

As BIA-ALCL is becoming more common in TGGD patients, surgeons should be aware of this and encourage follow up. Often patients experienced symptoms at least 2 years before going to their followed up, and with less frequency than cis-gender individuals[32]. Education of "signs and symptoms patients should look out for" may go a long way in improving rates of follow up as it makes patients aware of the dangers and gives them agency and involvement in their treatment.

Silicone Injections

Although it has been declared illegal since 1970s due to high number of complications, unfortunately free silicone injection has been and continues to be performed as a mode of breast augmentation in the TGGD individuals[50]. Secondary breast reconstruction after silicone injections is relevant to chest feminization. In one study, the incidence of prior silicone breast injections was 7.3%. In their cohort of 41 chest feminization surgery patients, there was only one patient with minor complications which healed without surgical intervention[51]. This study concluded that careful evaluation and planning can minimize the risk of complications in secondary breast reconstruction post silicone injections. Another study reported a case of TGGD patient with a false-positive axillary lymph nodes due to silicone adenitis from silicone leakage[52]. A final case reports two incidences TGGD patients with breast inflammation and necrosis as a result of silicone and paraffin injections[53].

A carefully performed history and physical exam are critical to planning reconstruction options. One point that was not discussed in these case reports is how silicone will affect breast imaging and routine cancer screening by obscuring the gland tissue. This has been addressed in the American College of Radiology (ACR) guidelines in more detail. Overall, successful reconstruction is possible as long as one familiarizes themselves with silicone usage and how it can mimic other pathologies. Patients with silicone may require further workup to ensure etiology of pathology before surgical planning can safely begin.

Uterine/Endometrial Cancer Screening

Figure 5 includes the PRISMA flow diagram regarding endometrial and cervical cancer studies. A lack of endometrial screening protocols for TGGD people on HRT, lead providers to follow the guidelines currently in place for cis-gender women. There is currently no evidence-based indication to perform prophylactic screening for endometrial cancer in cis-gender women. As such, diagnostic procedures like an endometrial biopsy or transvaginal ultrasound are not routinely recommended for transgender men regardless of hysterectomy status. Abnormal vaginal discharge and bleeding serve as signs to seek screening measures. The ACS recommends educating TGGD individuals with a vagina on the topic of unusual vaginal bleeding and to explore instances both pre and post hysterectomy. This may be difficult as TGGD individuals often avoid regular visits to their gynecologist, especially after undergoing a hysterectomy.

A uterine pathology study from Grimstad *et al*[54] reviewed 94 transgender men receiving testosterone therapy, reporting no case of endometrial cancer[55]. A similar pathologic analysis from Ralph *et al*[55] reported no evidence of malignant changes to the endometrium of transgender men in response to long-term testosterone treatment[55]. The uterine histological similarity to cis-gender women indicates regular endometrial screening is unlikely to be necessary for transgender men undergoing androgen therapy.

Uterine/Endometrial Cancer Treatment

The literature documents one case of uterine cancer in a transgender man after he was found to have a mass noted during speculum examination for planned hysterectomy in preparation for GAS[56]. Post-operative pathology from a transmasculine person's radical hysterectomy revealed stage IIIC endometrioid adenocarcinoma of the uterus. The diagnosis included involvement of the parametrium and lymph nodes. The patient was treated with 6 cycles of chemotherapy (carboplatin and paclitaxel) before declining additional treatment. Two years later, the patient had evidence of recurrent disease and underwent additional chemotherapy. Follow up beyond this date is lost. The authors note the potential importance of evaluating the endometrium prior to undergoing a hysterectomy as the surgery could have been altered to more effectively treat the adenocarcinoma.

Cervical Cancer Screening

At present, there are no specific guidelines for transgender men regarding cervical cancer screening. As such, providers currently follow the guidelines created for cis-gender women when conducting screening on transgender men. The current recommendation indicates any cis-woman over 21 years old should have a Pap smear performed every 3 years or a human papillomavirus (HPV) test performed every 5 years. Screening may stop if the patient no longer has a cervix or if the patient is 65 years old and testing had been normal over the previous 10 years. A partial or supracervical hysterectomy preserves the cervix, indicating that not all transgender men with hysterectomies should stop receiving regular cervical cancer screenings.

In some cases, a routine postoperative histology workup may reveal cervical carcinoma in situ. Dysplasia of the cervix can spread to the vagina, which indicates the need for continued screening of the vaginal fornices even post-hysterectomy. It follows that convincing TGGD patients to continue regular cancer screenings after their hysterectomy poses a challenge, most importantly when partial cervix tissue remains[57].

A possible solution exists, such as increasing the availability of self-collected HPV DNA tests. Goldstein *et al*[58] reported a 2-fold increase in transgender men receiving HPV testing after introducing self-collected HPV swabbing options[58]. Additional research shows self-collected HPV tests have a 71.4% sensitivity when compared to provider-

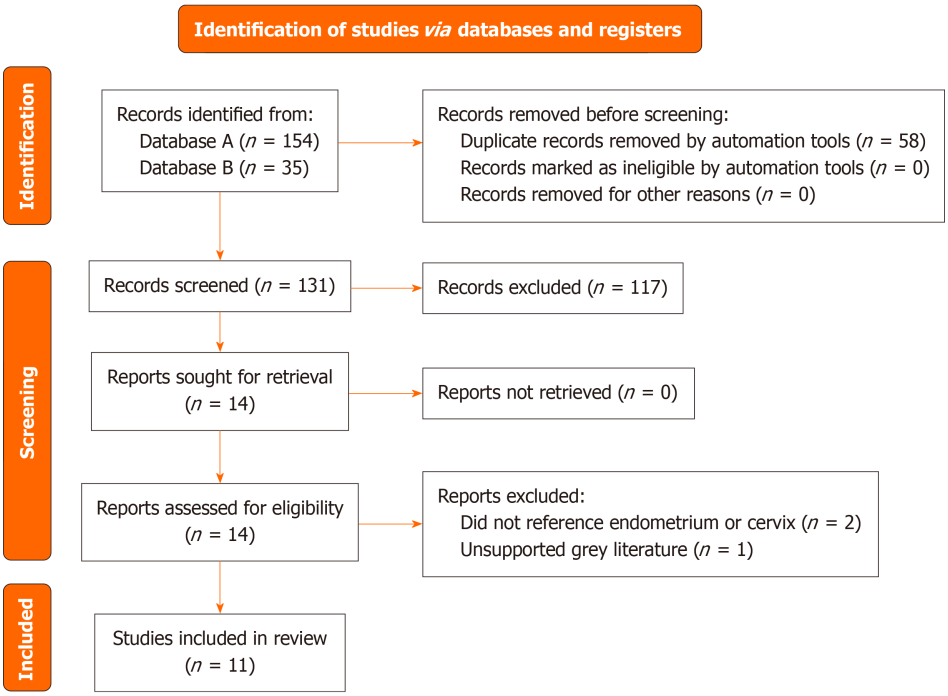

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Figure 5 The preferred reporting items for systematic reviews and meta-analyses flow diagram indicated database search records and inclusion decision steps. The diagram includes records regarding endometrial and cervical cancer studies.

collected HPV tests[59]. The efficacy is consistent with the rates seen in the cis-gender women population choosing to use self-collected swabs.

Adding to the complexity of cancer screening is the inconsistent correlation between exogenous testosterone use and the risk of carcinoma in the female reproductive system. There is a report of TGGD patients on androgens having higher rates of unsatisfactory or abnormal Pap smear results when compared to cis-gender women[60]. Contradicting this study are two recent publications that showed no significant difference between rates of epithelial cell abnormalities between transgender and cis-gender women receiving Pap tests[61,62]. Further studies must be done to determine the extent to which exogenous testosterone treatment can influence cell growth in cervical tissue.

Cervical Cancer Treatment

There are 3 reported cases of cervical cancer in transgender men documented in the literature. Driák and Šamudovský[63] report a case of localized squamous carcinoma, which was detected during a pathologic analysis of the cervix post-abdominal hysterectomy[63]. The patient had been on androgen therapy for the previous 4 years and did not need any oncological treatment beyond the hysterectomy. A case presented by Urban *et al*[56] follows a transgender man diagnosed with invasive stage IB adenoma malignum after receiving a laparoscopic total hysterectomy and bilateral salpingo-oophorectomy[56]. The patient reported vaginal bleeding for a 2-year period prior to the surgery, but contributed this to androgen therapy, which he had been on for the previous 7 years. He was subsequently treated with weekly cisplatin, external beam pelvic radiation, and intracavitary radiation to the upper vagina, which left him without evidence of disease. The most recent report of cervical carcinoma comes from Beswick *et al*[64], who present a transgender man diagnosed with stage IV A cervical cancer[64]. This 45-year-old patient had previously been on androgen therapy but stopped 18 mo prior to presenting with abnormal vaginal bleeding and subsequent squamous cell cervical carcinoma. The patient was treated with external beam radiation, weekly radiosensitizing cisplatin chemotherapy, and high-dose–rate intracavitary brachy-therapy. The patient showed no evidence of disease 6 mo after completing treatment. Ovaries see Figure 6.

Screening

Current screening guidelines state that there is no unique recommendation for TGGD individuals with ovaries. It is recommended that they follow the same guidelines established for cis-gender women: routine age-appropriate surveillance, a gynecological evaluation at least every 3 years (particularly for patients with a strong family history associated to ovarian cancer) with a pelvic examination, and routine ovarian cancer screening is not recommended[2,65].

Of the 13 articles included in our systematic review, seven described cases of ovarian cancer amongst TGGD and their respective management. There have been eight cases reported in the literature regarding cases of ovarian cancer amongst TGGD individuals, seven of whom had taken gender-affirming hormone therapy[66-72].

Cases in literature and their respective management: Figure 6 includes the PRISMA flow diagram regarding ovarian cancer studies. Hage *et al*[66] published the first journal article discussing two case reports about TGGD individuals who

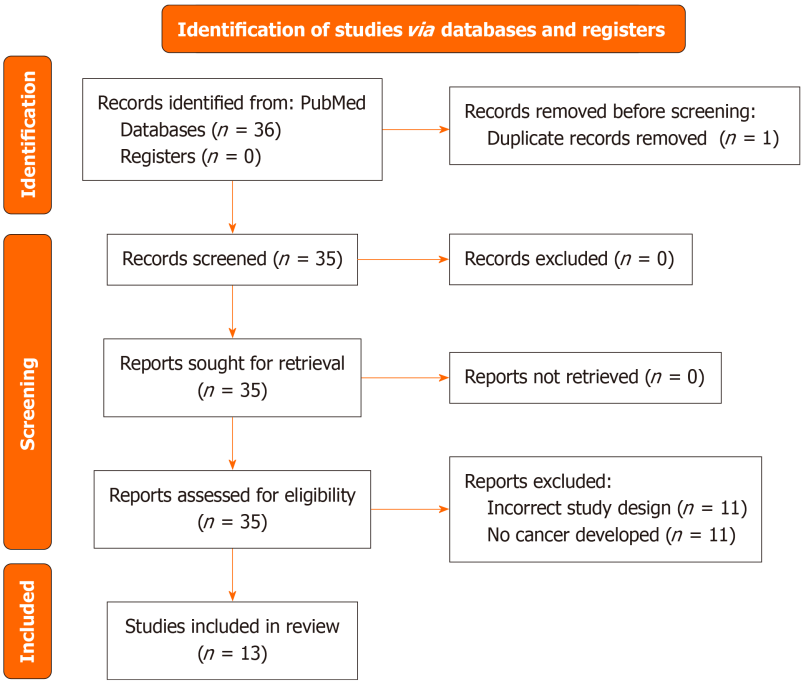

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Figure 6 The preferred reporting items for systematic reviews and meta-analyses flow diagram indicated database search records and inclusion decision steps. The diagram includes records regarding ovarian cancer studies.

were diagnosed with ovarian cancer. Patient A was diagnosed with papillary cystadenocarcinoma and underwent a laparotomy, supracolic omentectomy, and left oophorectomy followed by adjuvant combination chemotherapy with taxol, epirubicin, cis-platinum. Patient B was diagnosed with papillary borderline tumor in the left ovary, which was discovered as the patient was admitted to undergo a hysterectomy and bilateral salpingo-oophorectomy. Patient B eventually underwent a laparotomy and resection of multicystic mass. No radiotherapy or chemotherapy was required. In both cases reported, Patient A and Patient B had a history of hormone therapy reported[66].

The next case was reported by Dizon *et al*[67], which described a 46-year-old transgender man who was diagnosed with endometrioid adenocarcinoma arising in the left ovary and fallopian tube. This patient underwent a total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic node dissection, and peritoneal staging biopsies. Following surgery, chemotherapy was completed, consisting of carboplatin and paclitaxel. This case report also noted that the patient had used hormone therapy as part of their gender affirming surgery, but it was discontinued following surgery[67].

Another case report by Ferreira *et al*[68] described a 23-year-old transgender man with a history of testosterone therapy who was diagnosed with bilateral serous borderline ovarian tumor and underwent a total hysterectomy and bilateral salingo-oophorectomy. There was no discussion about subsequent chemotherapy[68].

Aubrey *et al*[69] published a similar case report about a 36-year-old transgender man diagnosed with stage IIA ovarian endometrium cancer who underwent a bilateral salpingo-oophorectomy followed by six cycles of chemotherapy. This patient also was using hormone therapy, which was discontinued after surgery[69].

Stevens and Abrahm[70] published another case report of a 67-year-old who was diagnosed with metastatic ovarian cancer and used exogenous testosterone. There was no mention about chemotherapy or surgery, and the patient remained in the hospital and received palliative care[70].

Bilash and Walker[71] published an article discussing Bilash's personal experiences as a transgender individual who was diagnosed with polycystic ovarian syndrome in his early 20s and underwent a bilateral oophorectomy and total hysterectomy at the age of 30 for stage III ovarian cancer. Bilash and Walker[71] began using testosterone therapy following surgery[71].

Millington *et al*[72] presented a case report about a 17-year-old transgender adolescent who was diagnosed with serous borderline ovarian tumor. The patient began subcutaneous testosterone cypionate 12 wk prior to the diagnosis. For treatment, the patient elected a right salpingo-oophorectomy. Post-operatively, testosterone was restarted two months following the procedure and surveillance of the remaining ovary was continued and eventually unremarkable over time [72].

Prevention and Management: As demonstrated by both the case reports and the current literature, there have been discussions about the possible relationship between using testosterone supplements and a potential increased risk of ovarian cancer. However, it has been repeatedly emphasized that there is currently a lack of reported cases and data in the TGGD community to prove the possible mitogenic effects of long-term exposure to exogenous androgens on ovaries [66,68,69,72,73].

This correlates to another topic that has been debated in the literature, which is the use of bilateral salpingo-oophorectomies as a possible preventative measure of ovarian cancer in the TGNC community. Currently, according to National Comprehensive Cancer Network guidelines for cis-gender women, TGGD who are carriers of the BRAA1 and BRCA2 mutation should be offered risk-reducing salpingo-oophorectomy. If patients chose to defer this procedure, serial monitoring is considered as an alternative[47]. Some articles explore the possibility of expanding preventative ovariectomies to TGGD patients who are eligible for gender-affirming surgery and are on hormone therapy (such as a simultaneous salpingo-oophorectomy for TGGD individuals who undergo hysterectomy)[66,74]. Other articles noted the lack of knowledge about the long-term effects of oophorectomy at the time of a hysterectomy and how oophorectomies affect the quality of life, gender dysphoria, and the risk reduction of ovarian cancer in the TGNC population[67,68,73,75]. Kwiatkowska *et al*[76] emphasizes the responsibility of the physician during hormone therapy, in which that gender-affirming surgeries must be beneficial for the overall well-being of the patient, which continues to remain a gray area due to the lack of research about the impact of hormone therapy on the risk of ovarian cancer and the benefits of prophylactic bilateral salpingo-oophorectomy in TGGD individuals using hormone therapy[76].

Overall current guidelines state TGGD individuals neither require routine ovarian cancer screening nor additional surveillance and prophylactic oophorectomies are not needed as TGGD individuals are not at an increased risk of ovarian cancer[2].

The healthcare needs of TGGD individuals are unique due to gender-affirming hormonal therapy and or surgical interventions. The most commonly used hormone therapies are antiandrogens combined with Estrogen. Subsequently, after 18–36 mo of hormone therapy[77], transgender women can undergo vaginoplasty, including orchiectomy. The Prostate usually is not removed during feminizing genital GAS (fgGAS) (vaginoplasty or vulvoplasty) due to potential significant complications such as incontinence. The permanence of the prostate after fgGAS poses a continued risk for prostate cancer.

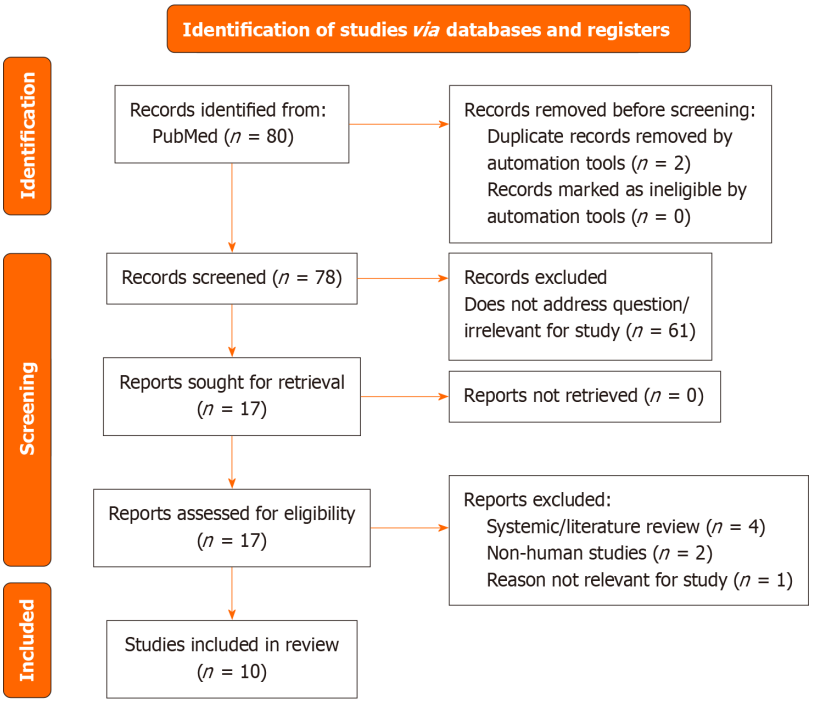
Antiandrogen and estrogen therapy with or without orchiectomy is theorized to have a lower incidence of prostate cancer in transgender women compared to cisgender men[78]. The main goal of hormone therapy is the regression of adult male sexual characteristics while inducing female sexual development in a transgender women with minimal long-term risk. While Estrogen has a short-term risk of thrombosis, the long-term risk of estrogen use is unclear[79]. Recent research has shown estrogen receptor–a, may have carcinogenic effects on the Prostate alone. A higher estradiol to dihydrotestosterone ratio may promote stromal cell growth in the prostate as well[79].

As part of antiandrogen treatment in male to female TGNC patients Prostate-specific antigen (PSA) and human glandular kallikrein (hK2) have been found to be elevated in plasma and urine after antiandrogen treatment in transgender women[80]. Both of these molecules are mainly produced by the Prostate, and androgens regulate their genes through the AR. Currently, screening guidelines for the TGGD population with prostates are the same as cis men. Transgender women 50 years and older should undergo annual prostate evaluation, consisting of digital rectal examination (DRE). Annual PSA evaluation might still have pertinence in prostate cancer screening and follow up. de Nie *et al*[81] performed a prostate biopsy in a transgender woman diagnosed with prostate cancer who had undergone orchiectomy with estrogen treatment[81]. The biopsy produced positive staining for prostate acid phosphatase (PAP) and prostate-specific antigen (PSA), showing that natural prostate activity persists in the castrated individuals and that this activity does not rely solely on androgens. As PSA is usually highly suppressed in these individuals following bilateral orchiectomy, any PSA value greater than 1.0 ng/mL should be regarded as concerning[82]. Further research on the adequate PSA monitoring threshold is required for this subset of patients.

A biopsy is a primary tool for diagnosing prostate cancer and determining a Gleason score for prognosis. Some studies have shown the difficulty of assigning a correct Gleason score due to morphologic changes to the Prostate induced by androgen deprivation adding a layer of complexity when interpreting results in the TGGD population[83]. For both cis men and transgender women diagnosed with prostate cancer multiple treatments are available. Amongst them include gonadotropin-releasing hormone (GnRH) agonists/antagonists, radiotherapy, chemotherapy, robotic-assisted laparoscopic prostatectomy, and cystoprostatectomy. New therapies such as abiraterone, enzalutamide, sipuleucel-T and cabazitaxel have been introduced to treat hormone-resistant prostate cancer[82].

In our review, we identified 14 TGGD individuals diagnosed with Prostate Cancer. Figure 7 includes the PRISMA flow diagram regarding prostate cancer studies. Of those 14, three underwent chemotherapy using estramustine, mitoxantrone, docetaxel, carboplatin, or prednisone. One patient underwent external beam radiotherapy, antiandrogen therapy, followed by mitoxantrone and prednisone, and passed away from a thromboembolic event[19]. Another patient underwent robotic-assisted laparoscopic prostatectomy and bilateral pelvic lymph node dissection[84]. One patient underwent cystoprostatectomy with resection of a right pelvic mass and lymph node dissection following chemotherapy with docetaxel and carboplatin[82]. Another patient was started with antiandrogen therapy using oral bicalutamide and oral dutasteride[82] one patient underwent radical radiotherapy and died after six months of therapy. Treatment for the other six patients was not discussed. There were only two reported deaths of the 14 reported Prostate cancer cases we identified.

The absence of TGGD-specific screening guidelines, unconfirmed effects of gender-affirming hormone therapy on prostate cancer, change of the pelvis anatomy following the surgery, and barriers of care by the healthcare providers and system can delay cancer diagnosis and treatment. The combination of factors may lead to poorer prognosis in this population[79]. Yet, although the incidence is lower in TGGD women, Jackson *et al*[79] have indicated that prostate cancer could be more aggressive amongst TGGD population with increased mortality amongst TGGD women. Incidence of prostate cancer after prolonged use of gender-affirming hormone therapy raises questions about the "protective" role of castrating status in cancer pathogenesis[85]. Further study regarding the effects of gender-affirming hormone therapy and orchiectomy is needed to shape the screening and treatment of Prostate cancer in TGGD women.



DOI: 10.5306/wjco.v14.i7.265

Figure 7 The preferred reporting items for systematic reviews and meta-analyses flow diagram indicated database search records and inclusion decision steps. The diagram includes records regarding prostate cancer studies.

Currently, the USPSTF recommends against regular screening for Testicular Cancer in cis-gender men and has no recommendations for TGGD population. Figure 8 includes the PRISMA flow diagram regarding testicular cancer studies. Some societies recommend annual self-examinations. In TGGD population, hormonal therapy (primarily estradiol) is instituted with the goal to develop female secondary sex characteristics. Estrogen is thought to be a risk factor for development of testicular cancer although no large-scale studies have been done that show a link.

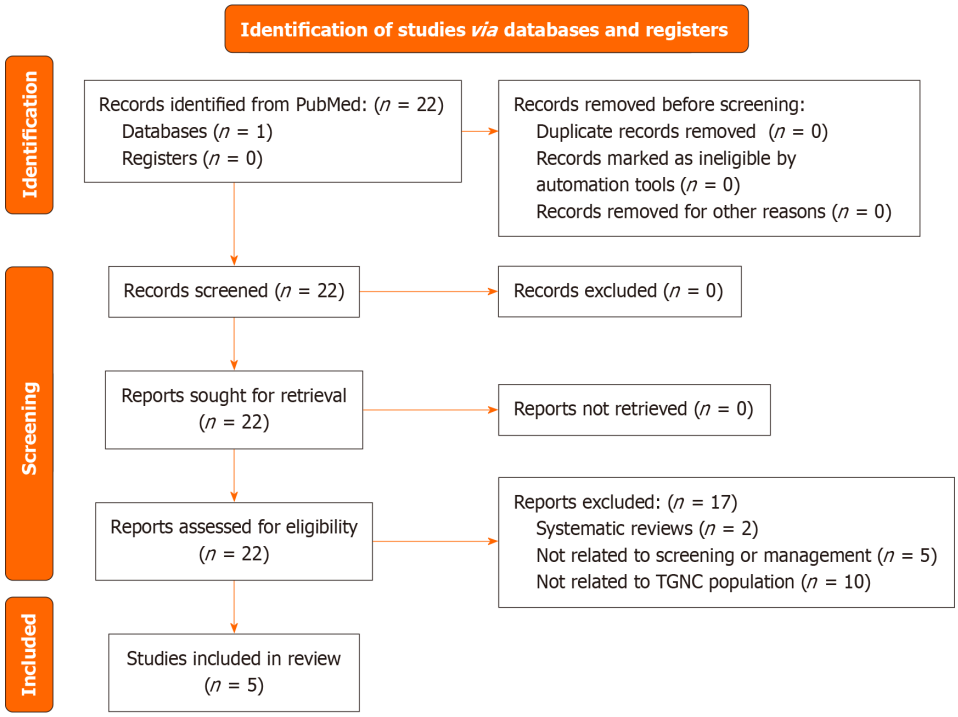
Standard management of testicular cancer involves tumor markers (β- human chorionic gonadotropin, Lactate Dehydrogenase (LDH) and alpha-fetoprotein), computed tomography scan of chest/abdomen/pelvis followed by radical orchiectomy. Tumor markers can help differentiate the type of cancer present, although standard of care involves a radical orchiectomy up front. Our review resulted in 5 cases of testicular cancer found in the TGGD population. Two cases were found when testosterone levels failed to suppress despite hormonal therapy. One case reported by Wolf-Gould and Wolf-Gould[86] was found to have an intratubular germ cells neoplasia (carcinoma in site), embryonal cell carcinoma[86]. Another case reported by Elshimy *et al*[87] was found to have a B-HCG secreting seminoma[87]. One case of seminoma reported by Kvach *et al*[88], was discovered incidentally after penile-inversion vaginoplasty[88]. A case by Chandhoke *et al*[89], reported a 38-year-old transgender woman with a testicular mass and a retroperitoneal tumor that was too morbid to resect[89]. The patient underwent radical orchiectomy followed by maintenance on chemotherapy and surveillance with serial imaging. An interesting case by Kobori *et al*[90] was revealed to have a mature testicular teratoma with positive estrogen receptor expression while undergoing hormonal therapy with estrogen and progesterone[90]. The authors note that although receptor expression does not necessarily imply causation, the contribution of estrogen cannot be ruled out. The patient elected to stop hormonal therapy in this case.

All patients underwent radical orchiectomy with chemotherapy reserved for patients who met criteria per cis-gender guidelines. Four patients elected to stop estrogen therapy; however, this was after an extensive discussion with the patient on the social and psychological effects of cessation.

DISCUSSION

Prior to breast cancer screening guidelines for the TGGD patient from the American College of Radiology in November 2021, no formal cancer screening guidelines were made for the TGGD population. In most instances, screening guidelines for the TGGD population default to cis-gender screening recommendations and management. Further, guidelines are needed to address non binary patients as existing literature in this select population is also lacking. Although screening suggestions based on this systematic review are alluded to in each organ section, the discussion of organ specific screening centers on a call to action for better research.

Discussion on cancer management is provided in each organ section in more detail. However, some overarching themes hold true for all cancer management. Provider education in the communication skills with the TGGD population in the form of gender friendly language is paramount to improve the existing barriers of care, improve healthcare access-



DOI: 10.5306/wjco.v14.i7.265

Figure 8 The preferred reporting items for systematic reviews and meta-analyses flow diagram indicated database search records and inclusion decision steps. The diagram includes records regarding testicular cancer studies. TGNC: Transgender and gender nonconforming.

ibility and increase provider options for these patients. Addressing the limitations of care and actively participating in scientific research for this population will allow for earlier detection of cancer, improved treatment adherence, improved patient care accessibility and ultimately improved patient follow up and satisfaction.

CONCLUSION

Currently, a comprehensive guideline for cancer screening in the TGGD population is lacking. Prior to breast cancer screening guidelines for this population from the ACR in November 2021, no formal cancer screening guidelines were made for the TGGD population. In most instances, screening guidelines defaulted to cis gender screening recommendations and management. However, caring for the TGGD population undergoing gender affirming surgery is highly individualized and requires consideration of factors such as the age at which they commenced hormonal therapy, the stage of transition, and the disproportionate social determinants of health these patients are subject to. For all these reasons, these patients are at higher risk of developing cancer and or having their cancer detected at a later, more aggressive stage because they do not have access to the appropriate and comprehensive care they require.

This study performed systematic review of the current literature surrounding both the screening and management of cancer in the transgender and gender diverse population whom are considering gender affirming surgery. In addition to calling for better education and evidence based guidelines for physicians to follow, this paper is a call to action for physicians to openly address the limitations of care and to actively participating in scientific research for this population to allow for earlier detection of cancer, improved treatment adherence, improved patient care accessibility and ultimately improved patient satisfaction.

ARTICLE HIGHLIGHTS

Research background

Lack of screening and management guidelines in the transgender and gender diverse (TGGD) and non binary population.

Research motivation

A comprehensive guideline for cancer screening in the TGGD population is lacking. Caring for the TGGD population undergoing Gender Affirmation Surgery is highly individualized and requires consideration for the whole, integral patient including the physical and psychological realm. Communication and access to care should strive for inclusion and

avoid potential discrimination from misgendering. Once diagnosed with cancer, TGGD patients should receive care at institutions capable of providing a multi-disciplinary approach. This collective approach will ensure record upkeep and help delay any unnecessary delays in care. Resolving the lack of guidelines, improving inclusion, and diminishing the barriers of care will ultimately lead to more timely and efficient care for the TGGD population.

Research objectives

Literature is lacking regarding screening and management guidelines in the TGGD and non binary population. Barriers of care are present and need to be addressed to improve access and quality of care for this population.

Research methods

A systematic review utilizing the preferred reporting items for systematic reviews and meta-analyses guidelines was used. Rayyan software was used to organize and collaborate on articles for reviewers. A systematic search of PubMed on January 5th, 2022, with the following terms: "TGNC", OR "transgender", OR "gender non-conforming", OR "gender nonbinary" AND "cancer screening", AND "breast cancer", AND "cervical cancer", AND "uterine cancer", AND "ovarian cancer", AND "prostate cancer", AND "testicular cancer", AND "surveillance", AND "follow-up", AND "management". After eliminating review articles, duplicates, abstracts, articles not relevant to the section topic or opinion pieces a total of 70 studies with original data were obtained. Articles relevant to the section topic, including the search terms were included in this systematic review. Search parameters were performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Two independent reviewers Araya S and Nannapaneni S carried out independent abstract revisions on January 11th, 2022, using systematic review software "Rayyan" registered in Cambridge Massachusetts.

Research results

Literature is lacking regarding screening and management guidelines in the TGGD and non binary population. Barriers of care are present and need to be addressed to improve access and quality of care for this population.

Research conclusions

Caring for the TGGD and nonbinary patients is a complex process and requires understanding of three key points – care is highly individual, it depends on stage of gender affirming surgery, and it is centered on proper provider education and training. An understanding of the biopsychosocial model of health, where illness must be considered from not only the physical body, but also from the psychological and social aspects is required. Prior to breast cancer screening guidelines for the TGGD patient from the American College of Radiology in November 2021, no formal cancer screening guidelines were made for the TGGD population. In most instances, screening guidelines for the TGGD population default to cis gender screening recommendations and management. Further, guidelines are needed to address non binary patients as existing literature in this select population is also lacking. Although screening suggestions based on this systematic review are alluded to in each organ section, the discussion of organ specific screening centers on a call to action for better research. Discussion on cancer management is provided in each organ section in more detail. However, some overarching themes hold true for all cancer management. Provider education in the communication skills with the TGGD population in the form of gender friendly language is paramount to improve the existing barriers of care, improve healthcare accessibility and increase provider options for these patients. Addressing the limitations of care and actively participating in scientific research for this population will allow for earlier detection of cancer, improved treatment adherence, improved patient care accessibility and ultimately improved patient follow up and satisfaction.

Research perspectives

Creating specific cancer screening and management guidelines for the TGGD and non binary population while improving barriers to care.

FOOTNOTES

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ORCID number: Juliet C Panichella 0009-0008-8478-7694; Sthefano Araya 0000-0002-8245-8036; Alireza Hamidian Jahromi 0000-0002-7585-847X.

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