ON THE
CUTTING EDGE
Diabetes Care and Education

Diabetes Care and Education
a dietetic practice group of the
Academy of Nutrition and Dietetics

Spring 2013 | Volume 34 | Number 2
A Peer-Reviewed Publication

Oncology Nutrition
Connection

Oncology Nutrition
a dietetic practice group of the
Academy of Nutrition and Dietetics

Spring 2013 | Volume 21 | No. 2
ISSN 1545-9896

Diabetes and Cancer: Addressing Interrelationships and Treatment Recommendations

Welcome to this special edition, joint newsletter of *On The Cutting Edge* and *Oncology Nutrition Connection!* The Diabetes Care and Education and the Oncology Nutrition Dietetic Practice Groups are excited to bring you this combined topic issue. We thank editors Diane Reader, RD, LD, CDE (OTCE) and Maureen Leser, MS, RD, CSO, LD (ONC) for their brilliant idea to create a collaborative newsletter covering both diabetes and cancer.

Over 25 million people in the United States have diabetes, and another 79 million are estimated to have prediabetes. There are nearly 14 million cancer survivors in the U.S., and that number is expected to rise to 18 million by 2022. And by 2020, two-thirds of cancer survivors will be aged 65 and older, an age group for which the prevalence of type 2 diabetes is significant. When we consider these facts and figures, it becomes evident that it will be the rare RD who isn't working with clients who are affected by both diabetes and cancer.

Also consider that diabetes and cancer share nutrition-related, etiologic pathways, which underlie the development of both conditions. Risk factors for these diseases often overlap, and cancer treatments may even increase the likelihood of weight gain and diabetes development. Indeed, any RD who works in the diabetes arena is likely to encounter clients with a history of cancer, and any RD working in oncology is similarly likely to have clients with diabetes.

Finally, we all know that "an ounce of prevention is worth a pound of cure." To be effective in our work, we must understand current disease prevention strategies for both diabetes and cancer. In this joint DCE and ON DPG newsletter, you will find articles that address all of these topics and more. You will gain valuable information to help you answer your patients' many questions regarding the diabetes/cancer connection and can use this newsletter as an excellent resource for promoting diabetes and cancer prevention.

Please let us know if you would like to see other DPG collaborations in the future – and what topics you would like to see addressed.

Warm regards,

Andrea Dunn, RD, LD, CDE
DCE DPG Chair

Suzanne Dixon, MPH, MS, RD
ON DPG Chair

ON THE
CUTTING EDGE
Diabetes Care and Education

eat right. Academy of Nutrition and Dietetics

*News*FLASH and *On the Cutting Edge* are bi-monthly publications of the Diabetes Care and Education (DCE) Dietetic Practice Group of the Academy of Nutrition and Dietetics (the Academy).

Print Communications Coordinator:
Liz Quintana, EdD, RD, LD, CDE

***News*FLASH Editor:**
Lorena Drago, MS, RD, CDN, CDE

***On the Cutting Edge* Editor:**
Diane Reader, RD, CDE

***On the Cutting Edge* Associate Editor:**
Sue McLaughlin, MOL, RD, LMNT, CDE

Subscriptions are available for people who are ineligible for the Academy membership for $30 (domestic), $35 (international) by sending a check to:

Linda Flanagan Vahl
DCE Administrative Manager
Academy of Nutrition and Dietetics
120 South Riverside Plaza, Suite 2000
Chicago, IL 60606-6995

Payable to Academy of Nutrition and Dietetics/DCE noting preferred mailing address.

Library of Congress National Serials Data Program ISSN #1070-5945, issued 7/93.

Table of Contents

Oncology Nutrition Connection

A publication of Oncology Nutrition (ON), a dietetic practice group of the Academy of Nutrition and Dietetics ISSN 1545-9896

Visit the ON DPG website at www.oncologynutritiondpg.org

Editor:
Maureen Leser, MS, RD, CSO, LD
mgoreleser@gmail.com

Associate Editors:
Maureen Boswell, RD, CSO, CDE
mboswell@wvmedical.com

Alicia Merritt, MS, RD, CSO, LD
Aliciard12@gmail.com

Jocelyne O'Brien, MPH, RD, CSO, LD, CNSD
jocelynenasser@yahoo.com

Oncology Nutrition Connection (ONC) ISSN 1545-9896), the official newsletter of the Oncology Nutrition Dietetic Practice Group, is published quarterly. The spring 2013 issue has been approved by the Academy of Nutrition and Dietetics for 3.0 CPEs. To obtain 3.0 CPEs for this issues:

1. Read the entire issue
2. Answer the CPE review questions
3. Compare your answers to the answer key posted in the newsletter. Credit is awarded to RDs who correctly answer eight of the questions.
4. Once you have correctly answered eight questions, log onto the ON website (newsletter section) to access and print the CPE certificate. You are responsible for recording 3.0 CPEs in your Professional Development Portfolio (PDP).

All issues of *Oncology Nutrition Connection* are distributed in electronic format only. Viewpoints and statements in this issue do not necessarily reflect the policies and/or positions of the Academy of the ON DPG.

Members are responsible for recording and tracking their CPEs in their Professional Development Portfolio (PDP) in accordance with PDP guidelines.

Articles published in *ONC* highlight specific diseases or areas of practice in oncology nutrition. All issues of *Oncology Nutrition Connection* are distributed in electronic format only. Viewpoints and statements in this issue do not necessarily reflect the policies and/or positions of the Academy or the ON DPG. Oncology dietitians are encouraged to review Evidence Analysis Library (EAL®) positions of the Academy of Nutrition and Dietetics, which provide a summary of the best available research on a variety of topics, via the Academy's website and at http://www.oncologynutrition.org/oncology-resources/evidence-analysis-library.

Oncology Nutrition Connection is indexed in the Cumulative Index to Nursing and Allied Health Literature. For inquiries regarding copyright, single- issue sales, and previous issues, contact the editor. Individuals interested in submitting a manuscript to *Oncology Nutrition Connection* should contact the editor or check the ON website for author guidelines. Individuals who are ineligible for membership in the Academy of *Nutrition and Dietetics can order yearly subscriptions to Oncology Nutrition Connection* for $35.00 (domestic fee) and $40.00 (international fee), payable to the Academy of Nutrition and Dietetics/ON DPG. Institutions can subscribe to *Oncology Nutrition Connection* for $50.00 (domestic yearly fee) and $65.00 (international yearly fee). ON DPG members have access to archived back issues in pdf format. Printed copies of back issues can also be ordered (when available) at a cost of $5.00 each for domestic ON DPG members ($10.00 if mailed internationally) and $10.00 each for domestic non-members ($15.00 each if mailed internationally). Send requests for subscriptions or back issues to the editor. All ON DPG member mailing address changes and email address changes should be sent to the Academy using the address change card in the Journal of the American Nutrition of Nutrition and Dietetics or at www.eatright.org in the members-only section.

Nutrition Therapy for the Prevention of Diabetes and Cancer

Marion J. Franz, MS, RD, CDE and Jocelyne O'Brien, MPH, RD, CSO

Abstract

Lifestyle choices can influence the risk of both cancer and diabetes. Common risk factors include age, glycemia, obesity, physical activity, gender, smoking, diet, and alcohol use. Many strategies that reduce the risk of cancer also decrease the risk of diabetes. For cancer prevention, encouraging individuals to maintain a weight within normal range, perform physical activity, and choose mostly a plant-based diet, which includes a variety of fruits, vegetables, whole grains and legumes while limiting energy-dense foods is key. In individuals with prediabetes, lifestyle interventions including modest weight loss (5-7% of body weight) and moderate physical activity (equivalent to 30 minutes of brisk walking on most days of the week) are effective in decreasing the risk of converting to diabetes by 29-67%.

Introduction

Cancer and diabetes are both leading causes of death worldwide, and are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age (1). Type 2 diabetes and cancer share many common potential risk factors. Nonmodifiable risk factors common to both are age, gender, family medical history, genetics, and race/ethnicity. Modifiable risk factors include obesity, diet, physical inactivity, tobacco smoking, and alcohol use (1). However, potential mechanisms that mediate these associations have yet to be determined. Under investigation are the involvement of growth hormone, insulin-like growth factor (IGF-1), and insulin on tumor promotion and progression (2).

Although genetic susceptibility influences the risk of cancer, most of the variation in cancer risk across populations and among individuals is reported to be due to factors that are not inherited. Behaviors such as avoiding exposure to tobacco products, limiting or avoiding alcohol, maintaining a healthy weight, staying physically active throughout life, and consuming healthy foods can substantially reduce an individual's lifetime risk of developing or dying from cancer (3). Genetic factors also affect the risk for diabetes, but in individuals with prediabetes, modest weight loss (5% to7% of body weight) and moderate physical activity (equivalent to 30 minutes of brisk walking on most days of the week) have been shown to decrease the risk of converting to diabetes by 29% to 67% (4). Furthermore, the impact of maintaining lifestyle interventions in preventing and/or delaying the onset of type 2 diabetes can persist for at least 10 years (4).

Changing Modifiable Risk Factors

Intentional Weight Loss

Evidence suggests that weight gain is associated with an increased risk of some cancers, including cancers of the breast, esophagus, colon, pancreas, and prostate (5). Weight gain is also associated with insulin resistance and type 2 diabetes, and numerous studies have shown that weight loss decreases diabetes incidence and has the potential to restore euglycemia (6-7). The American Diabetes Association (ADA) recommends weight loss for all overweight or obese individuals who are at risk for diabetes (7).

It is estimated that in the United States (U.S.) overweight and obesity contributes to 14% to 20% of all cancer-related mortality (3). The American Cancer Society (ACS) recommends that individuals be as lean as possible throughout life without being underweight and avoid excess weight gain at all ages (3,8). The association between weight loss and subsequent cancer risk is less clear (1). A summary of the association of weight loss following bariatric surgery and cancer incidence noted limited evidence for the benefit of reducing cancer risk with weight loss (9). Although more research is needed on how weight loss changes cancer risk, intentional weight loss may reduce the risk of postmenopausal breast cancer, and possibly other cancers (10). The ACS states that for those who are currently overweight or obese, losing even a small amount of weight has health benefits and is a good starting point. An initial goal of 5% to 7% weight loss is generally recommended (8).

Physical Activity

Epidemiologic studies consistently show that higher levels of physical activity are associated with lower risk of colon, postmenopausal breast, and endometrial cancer (5,11), but a clear link between physical activity and other cancers has not been established. The protective role for increased physical activity in preventing and treating diabetes has been established (12).

Recommendations are that all adults perform at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (12). Additional health benefits, including improved weight loss/maintenance, can be attained by increasing to 300 minutes (5 hours) per week of moderate-intensity or 150 minutes (2.5 hours) per week of vigorous-intensity aerobic activity. Muscle-strengthening activities, such as resistance training, that involve all major muscle groups should be performed on 2 or more days per week.

(Continued on page 5)

Table 1. Lifestyle Recommendations for the Prevention of Diabetes and Cancer (3,5,6)

Recommendations	American Diabetes Association	American Cancer Society, American Institute for Cancer Research
Body Weight	• Structured programs that emphasize lifestyle changes, including moderate weight loss (7% body weight) • Weight loss, if recommended, for all overweight and obese individuals • Dietary strategies that include reduced calorie and dietary fat are recommended	• Achievement and maintenance of a healthy weight throughout life • Maintenance of leanness throughout life without being underweight • Avoidance of excess weight gain at all ages; for those who are overweight or obese, losing even a small amount of weight has health benefits and is a good starting point • Regular physical activity and limited intake of high-caloric foods and drinks to maintain a healthy weight
Physical Activity	• Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintaining weight loss • Regular physical activity (150 min/week)	• At least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity each week (or a combination of these), preferably spread throughout the week (30 minutes every day) • Limiting of sedentary behavior such as sitting, lying down, watching TV, and forms of screen-based entertainments
Fiber	• Attempt to achieve the United States Department of Agriculture recommendations for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (50% of grain intake)	• Consumption of whole grains instead of refined grain products
Fruits and Vegetables		• Consumption of at least 2½ cups of vegetables and fruits each day • Consumption of a variety of vegetables, fruits, whole grains, and legumes such as beans
Red Meat and Processed Meats		• Consumption of no more than 18 oz (cooked weight) per week of red meats such as beef, pork, and lamb and avoidance of processed meat such as ham, bacon, salami, hot dogs, and sausages
Sugar-sweetened Beverages	• Limited intake of sugar-sweetened beverages	• Avoidance of sugary drinks • Limited consumption of energy-dense foods
Alcohol	• If individuals choose to drink alcohol, limit intake to a moderate amount (1 drink per day or less for adult women and 2 drinks or less per day for adult men)	• If consumed at all, limit to 1 drink per day for women and 2 drinks per day for men
Tobacco	• Avoid smoking • Include smoking cessation counseling and other forms of treatment as needed	• Avoid smoking or chewing tobacco

Healthy Eating Pattern

A number of studies suggest that a predominantly plant-based eating pattern emphasizing a wide variety of vegetables, fruits, whole grains, and legumes and lower intake of red and processed meat is associated with a lower risk of many types of cancers (3,5). Foods high in dietary fiber may protect against colorectal cancer and also provide a wide range of nutrients and phytochemicals that may act in a variety of pathways, possibly synergistically, to reduce the development of many cancers (5).

Randomized, controlled trials (RCTs) of nutrition interventions for diabetes prevention document benefits from low-fat, low-calorie diets plus-minus high-fiber diets (6). Since completion of the trials, several reviews of observational studies have demonstrated an inverse relationship for the risk of type 2 diabetes and consumption of whole grains, although the number of RCTs is limited (4). The Dietary Guidelines Advisory Committee (DGAC) 2010 states that limited evidence supports the association of whole grain consumption with reduced risk of type 2 diabetes (13). The committee also concluded that strong evidence suggests that a diet high in saturated fatty acids and trans fatty acids is associated with increased markers of insulin resistance and risk for type 2 diabetes, whereas unsaturated fatty acid intake is inversely associated with risk of diabetes. Cohort studies and a clinical trial have also reported an inverse risk of diabetes with adherence to a Mediterranean-style diet, an eating pattern that for some persons may be a palatable alternative to the low-fat diets used in diabetes prevention trials (4).

Of interest is a study showing that a combination of healthy lifestyle factors lowers the risk of developing type 2 diabetes (14). Results from the study of 207,479 people in the National Institutes of Health/American Association of Retired People (NIH AARP) Diet and Health Study revealed that participants who adhered to all five healthy lifestyle factors (a healthy eating pattern, participation in regular physical activity, maintaining a normal body weight, moderate alcohol intake, and being a nonsmoker) reduced their risk of developing type 2 diabetes by as much as 84% for women and 72% for men (14).

Because energy-dense and sugary foods contribute to overweight and obesity, the ACS, the World Cancer Research Fund/ American Institute for Cancer Research, and the ADA recommend limiting consumption of these foods (3,5,6). Based on evidence, the ADA specifically recommends limiting intake of sugar-sweetened beverages (6).

The ADA recommendations for primary prevention of diabetes (6) along with the ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention (3) and the World Cancer Research Fund/American Institute for Cancer Research (5) recommendations for a healthy lifestyle to prevent cancer are summarized in Table 1.

Alcohol

Alcoholic beverage consumption, even in moderate amounts, has been shown to increase the risk of many types of cancers, including those of the oral cavity, pharynx, larynx, esophagus, liver, colon/rectum, and female breast (15). The biologic mechanisms by which alcohol consumption may lead to cancer are not fully understood (3). Alcohol consumption may increase blood concentrations of estrogens or other hormones that increase breast cancer risk; reducing alcohol consumption is a widely recognized method of reducing the risk of breast cancer.

While excess alcohol consumption is a risk factor for diabetes, moderate alcohol consumption is associated with reduced diabetes incidence (4) and has been shown to increase insulin sensitivity. The ADA, ACS, and DGAC all recommend that if persons choose to drink alcoholic beverages, they should limit their intake to up to 1 drink per day for women and up to 2 drinks per day for men. However, they also caution that evidence does not support recommendations for individuals who are not currently consuming alcohol to start doing so based on potential benefits.

Tobacco Use

Tobacco use is clearly related to the development of many cancers (1). Smoking is also an independent risk factor for the development of diabetes (16), and has an adverse effect on diabetes-related complications (17).

Metformin

Metformin, which is commonly used in the management of type 2 diabetes, reduces insulin resistance, improves glycemic control, and can be combined safely with other antidiabetic drugs. In recent years, observational studies have suggested that metformin may be useful in the prevention and treatment of cancer due to its potential to inhibit the growth of cancer cells (18-19). However, this relationship has been questioned because of important methodological shortcomings in these studies (20-22). The studies are mostly retrospective and nonrandomized; metformin concentrations used in many experiments exceed those achieved with conventional doses used for diabetes treatment; and the studies have time-related biases. Therefore, further research is needed to evaluate any potential anticancer benefit of metformin.

Summary

Recommendations for weight management, physical activity, and a healthy eating pattern for diabetes and cancer prevention have many similarities. Clinicians in each specialty appreciate the importance of engaging in regular physical activity and maintaining weight within normal ranges for prevention of both diseases. However, cancer health organizations emphasize the importance of consuming a plant-based diet and

(Continued on next page)

limiting or avoiding alcohol intake, while moderate alcohol intake has been associated with a reduced risk of type 2 diabetes. Of note, the ACS and ADA guidelines for prevention of cancer and diabetes are consistent with those published by the American Heart Association (23) for the prevention of coronary heart disease and those for general health promotion, as defined by DGAC 2010 (13) and the 2008 Physical Activity Guidelines for Americans (12). For the public to experience health benefits from these recommendations, it is essential for RDs to promote their dissemination and implementation.

Marion J. Franz, MS, RD, CDE, is owner and director of Nutrition Concepts by Franz, Inc. in Minneapolis, MN

Jocelyne O'Brien, MPH, RD, CSO, specializes in clinical oncology nutrition in Wilmington, MA and is Associate Editor of *Oncology Nutrition Connection*, the newsletter of the Oncology Nutrition Dietetic Practice Group.

References

1. Giovannuci E, Harlan DM, Archer MC, et al. Diabetes and cancer. A consensus report. *Diabetes Care*. 2010;33(7):1674-1685.
2. Clayton PE, Nanerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol*. 2011;7(1):11-24.
3. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62(1):30-67.
4. Youssef G. Nutrition therapy and prediabetes. In: Franz MJ, Evert AB, eds. *American Diabetes Association Guide to Nutrition Therapy for Diabetes*. 2nd ed. Alexandria, VA: American Diabetes Association; 2012:469-499.
5. World Cancer Research Fund, American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, Second Expert Report 2012*. http://www.dietandcancerreport.org/. Accessed October 2012.
6. American Diabetes Association. Standards of medical care in diabetes—2012. Position statement. *Diabetes Care.* 2012;35(suppl 1):S11-S63.
7. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). Diabetes Prevention Program (DPP). National Diabetes Information Clearinghouse (NDIC). http://diabetes.niddk.nih.gov/dm/pubs/preventionprogram/ Revised November 6, 2012. Accessed March, 2013.
8. Rock CL, Boule C, Demark-Wahnerfried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012; 62(4):242-274
9. Renehan AG. Bariatric surgery, weight reduction, and cancer prevention. *Lancet Oncol*. 2009;10(7):640-641.
10. Byers T, Sedjo RL. Does intentional weight loss reduce cancer risk? *Diabetes Obes Metab.* 2011;13(12):1063-1072.
11. Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. *Med Sci Sport Exerc*. 2003;35(11):1823-1827.
12. United States Department of Health and Human Services. Physical Activity Guidelines Advisory Committee Report, 2008. http://www.health.gov/PAGuidelines. Accessed October 2012.
13. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010. http://www.cnpp.usda.gov/dgas2010-dgareport.htm. Accessed October 2012.
14. Reis JP, Loria CM, Sorlie PD, et al. Lifestyle factors and risk of new-onset diabetes: a population-based cohort study. *Ann Intern Med*. 2011;155(5):292-299.
15. Secretan B, Straif K, Baan R, et al. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol.* 2009;10(11):1033-1034.
16. Willi C, Bodenmann P, Ghali WA, et al. Active smoking and the risk of type 2 diabetes. A systematic review and meta-analysis. *JAMA*. 2007;298(22):2654-2664.
17. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. *Diabetes Care.* 1999;22(11):1887-1898.
18. Buzzai M, Jones RG, Amaravadi RK, et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. *Cancer Res.* 2007;67(14):6745-6752.
19. Thakkar B, Aronis KN, Vamvini MT, et al. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism. 2013 Feb 15. pii: S0026-0495(13)00018-8. doi: 10.1016/j.metabol.2013.01.014. [Epub ahead of print]
20. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. *Cancer Discov.* 2012;2(9):778-790.
21. Suissa S, Azoulay L. Metformin and the risk of cancer. Time-related biases in observational studies. *Diabetes Care.* 2012;35(12):2665-2673.
22. Smiechowski BB, Azoulay L, Yin H, et al. The use of metformin and the incidence of lung cancer in patients with type 2 diabetes. *Diabetes Care*. 2013;36(1):124-129.
23. Lichtenstein AH, Appel IJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114(1):82-96.

Health Connections Between Diabetes and Cancer

Lesley Fels Tinker, PhD, RD

Abstract

Reports of diabetes as a cancer risk factor surfaced during the 1980s and 1990s, around the same time that overweight and obesity rates in the United States (U.S.) began rising. Obesity was increasingly observed as a risk factor for cancer as well. All-cause mortality may be higher among cancer survivors with diabetes compared with cancer survivors who do not have diabetes. Obesity increases the risk of developing both diabetes and cancer, suggesting that attaining and maintaining a healthy body weight by balancing food intake with physical activity may decrease cancer risk among persons with diabetes. Blood glucose management using metformin or sulfonylureas has been associated with decreased cancer risk, whereas thiazolidinedione (pioglitazone) and insulin therapy may increase cancer risk. The association between the insulin analog glargine and cancer risk remains controversial, although recent evidence suggests that glargine does not increase cancer risk. The diabetes-cancer connection is complicated, and more research is needed to further elucidate common etiologic pathways underlying these two chronic diseases.

Introduction

As early as 1910, the medical biostatistician GD Maynard discovered correlations in death rates between diabetes and cancer in the U.S. (1). Even earlier, in 1885, a report was published describing correlations between cancer and diabetes (2). Research into links between diabetes and cancer progressed slowly during the early and mid-20th century, before increasing in the 1980s, followed by exponential growth in the 1990s, 2000s, and continuing through the present day. Investigations cover the full cancer spectrum, including the connections between diabetes and cancer incidence, recurrence, survival and mortality.

Current research suggests that type 2 diabetes (abbreviated in this article as diabetes) increases the risk of several cancers including breast (3), colorectal (4-6), endometrial (4), liver (4-5), and pancreatic (4-6). Prostate cancer risk stands alone as not being influenced by diabetes (4,8). Obesity, diet and physical inactivity are increasingly recognized as risk factors common to developing both diabetes and cancer (4). A number of diabetes-related factors intersect with the etiology and development of cancer, including treatment with insulin, metformin, sulfonylureas, or thiazolidinediones. The purpose of this article is to review evidence that examines connections between the incidence, mortality, lifestyle, and treatment modalities of diabetes and cancer.

Incidence

A meta-analysis of 39 independent risk estimates from observational studies suggests that breast cancer incidence in women with diabetes is 27% higher (95% Confidence Interval (CI): 1.16-1.39) than in women without diabetes (3). Neither pre-menopausal women nor women with type 1 diabetes exhibited increased breast cancer risk, whereas in ten studies examining postmenopausal women, risk was 15% greater among those with diabetes when compared with those without diabetes (95% CI: 1.07-1.24) (3). When limited to studies specifying type 2 diabetes (n=14), risk of breast cancer increased by 16% (95% CI: 1.04-1.29) compared with women without type 2 diabetes (3).

Other evidence supports the association of higher BMI with cancer incidence, implying that higher BMI is a reasonable surrogate for body fatness in the general population. Systematic review and meta-analysis of 221 datasets from 141 published papers (9) demonstrate that a 5-point increase in BMI for men and women is associated with higher risk of a number of tumor types. For men, authors reported strong associations between a 5-point increase in BMI and higher incidence of esophageal adenocarcinoma (Relative Risk (RR) 1.52, $p<0.0001$), thyroid (RR 1.33, $p=0.02$), colon (RR 1.24, $p<0.0001$), and renal (RR 1.24, $p<0.0001$) cancers (9). For women, authors reported strong associations between a 5-point increase in BMI and esophageal adenocarcinoma (RR 1.51, $p<0.0001$), endometrial (RR 1.59, $p<0.0001$), gallbladder (RR 1.59, $p=0.04$), and renal (RR 1.34, $p<0.0001$) cancers (9).

Duggan and colleagues found that two obesity-related factors were associated with breast cancer mortality (10). Homeostatic model assessment (HOMA), which measures hyperinsulinemia (10-11), was significantly and positively associated with breast cancer mortality when analyzed as a continuous variable (Hazard Ratio (HR) 1.12; 95% CI, 1.05 to 1.20) (10). Adiponectin is a hormone produced in adipose (fat) tissue that helps regulate blood glucose levels. Adiponectin levels above the median were associated with a decreased risk of breast cancer mortality (HR 0.39; 95% CI: 0.15 to 0.95) (10). Further, hyperinsulinemia, often associated with obesity, may stimulate proliferation of cancer cells (4).

Gastrointestinal cancers, which include esophageal, stomach, biliary tract, colon, rectal, pancreatic and liver cancer, also are linked with diabetes. Diabetes increases colorectal cancer risk in men and women (5-7), particularly at older ages. In a

(Continued on next page)

sub-study of postmenopausal women with diabetes who were enrolled in the Women's Health Initiative (WHI), data suggested that diabetes (when present at enrollment) was associated with an increased risk of colon (HR 1.38; 95 % CI: 1.14-1.66), rectal (HR 1.87; 95 % CI: 1.22-2.85), pancreatic (HR 1.62; 95 % CI: 1.15-2.30) and liver (HR 2.97; 95 % CI: 1.66-5.32) cancers (5). Diabetes medication also influenced risk of certain cancers in the WHI with metformin use increasing the risk of pancreatic cancer (HR 3.32; 95% CI: 1.74-6.32), an association not commonly observed. In this study insulin increased the risk of liver (HR 3.21;95% CI: 1.22-8.44), colon (HR 1.41; 95% CI: 1.01-1.98), rectal (HR 2.70; 95% CI: 1.39-5.23) and pancreatic cancer (HR 2.39; 95% CI: 1.39-4.09) (5).

Results for lung cancer are mixed. A review of medical records in the United Kingdom (UK) found no association between diabetes and lung cancer risk (12). However, in a large study of postmenopausal women, lung cancer risk was 27% higher (95% CI: 1.02-1.59) among women with self-reported, treated diabetes compared with women without diabetes (13). Further, in a cohort of postmenopausal women with diabetes, use of insulin was associated with a 71% higher risk (95% CI: 1.15-2.53) of lung cancer when compared with nonuse of insulin (14). Metformin, a biguanide believed to disrupt cellular energy systems and reduce the risk of cancer among persons with diabetes (14-17), was not associated with risk of lung cancer among adults in the UK (18), even with long-term usage (19).

Prostate cancer risk is generally lower in men with diabetes than in those without diabetes (20-23). Lower androgen levels, which may confer protection against cancer development, have been observed in men with diabetes (24). However, in a large Swedish population, the risk of prostate cancer was 9% greater among men with diabetes (Standardized Incidence Ratio (SIR) 0.91; 95% CI: 0.87-0.94), but that risk increased to 18% among men hospitalized for diabetic complications (SIR 0.82; 95% CI: 0.74-0.91), suggesting that inadequate glucose control may increase cancer risk (22). In Taiwan, where the incidence of prostate cancer is on the rise, diabetes was also associated with a higher risk of prostate cancer (RR 5.83; 95% CI: 5.10-6.66), particularly among a large, young cohort 40-64 years of age (RR 2.09; 95% CI: 1.60-2.74) (23).

Mortality

All-cause mortality has been reported to be 9-49% higher among persons with cancer and diabetes as compared with cancer survivors without diabetes (25-28). When examining the link between diabetes and survival after a cancer diagnosis, several factors should be considered, including cancer stage, cancer treatment and diabetes treatment. In a systematic review by Peairs et al. (28), women with diabetes who were diagnosed with breast cancer presented at a more advanced stage and experienced more toxic effects of chemotherapy compared with women without diabetes. In a retrospective study of 112,408 men and women (7.5% diabetes prevalence) in the United Kingdom, Currie et al. examined survival among those with diabetes who were diagnosed with a solid-tumor cancer. Although cancer mortality was increased in those with diabetes (HR 1.09; 95% CI: 1.06-1.13), diabetes therapy influenced survival (26). Treatment with sulfonylureas or insulin increased mortality (HR 1.13; 95% CI: 1.05-1.21; HR 1.13; 95% CI: 1.01-1.27 respectively), whereas use of metformin was associated with a lower mortality risk (HR 0.85; 95% CI: 0.78-0.93) (26). However, readers should not assume that mortality in those who have both diagnoses is always due to cancer, because cancer-specific mortality findings are mixed among persons with diabetes (28). Other causes of death are relevant.

In a cohort of Danish women, obesity (BMI ≥30) was found to be an independent predictor of increased risk of breast cancer metastases and all-cause mortality. BMI >30 increased the risk of distant metastasis after 5-10 years of follow-up (HR 1.46; 95%CI: 1.11-1.92) and increased all-cause mortality after 10-years of follow-up (HR 1.38; 95% CI: 1.11-1.71) (29). BMI did not exert an effect on local breast cancer recurrence.

Biological Connections Between Obesity and Cancer

Obesity, which has long been associated with diabetes and heart disease, may be a common underlying factor for the development of both cancer and diabetes. This connection may be related to insulin resistance with higher HOMA having been associated with increased breast cancer mortality (10). Insulin-like growth factor (IGF), hyperinsulinemia, and higher levels of steroid hormones and inflammatory markers also may connect obesity, diabetes and cancer (30). Further, body fat is the predominant source of estrogen in postmenopausal women, theoretically due to conversion of androgens to estrogens in adipose tissue (31). Cell studies suggest that estrogens increase cell proliferation in both healthy and malignant breast tissue (32). Research also suggests that insulin may stimulate growth of estrogen receptor-positive (ER+) breast cancer cells, while hyperinsulinemia contributes to synthesis of IGF I and II, which are believed to inhibit apoptosis (i.e. death) of cancer cells (33).

Lifestyle Components

Diet and physical activity may modify the risk of cancer among overweight and obese individuals. The American Institute for Cancer Research (AICR) states that one-third of the most common cancer types and approximately 25% of overall cancer diagnoses may be prevented by healthy patterns of diet and physical activity (34). Among men and women from the Health Professionals Follow-up Study and Nurses' Health Study, BMI was significantly associated with the risk of pancreatic cancer (35). Men and women with BMIs > 30 were more than 70% more likely to be diagnosed with pancreatic cancer when compared with men and women with BMIs < 23; RR for men was 1.76 (95% CI: 0.9-3.45) for pancreatic cancer for BMI > 30 compared with BMI < 23 and RR for women was 1.72; 95% CI: 1.19-2.48) for the same BMI comparisons. A slight inverse association between physical activity and risk of pancreatic cancer was observed in these cohorts, but was not statistically significant (35). Physical

inactivity has been linked with increased risk of coronary heart disease, diabetes, and both breast and colorectal cancer (36).

Diet may have a variety of effects on cancer risk, including modification of inflammatory factors. For example, higher intakes of red meat have been associated with higher levels of the inflammatory marker high sensitivity C-reactive protein (hsCRP) whereas higher intakes of whole grains have been associated with lower levels of this marker (37). The effect of dietary fat intake remains unclear. In the WHI, the 9% reduction in the incidence of postmenopausal breast cancer seen among those consuming a low-fat dietary pattern was not statistically significant. However, in subgroup analyses, women who started with higher fat intakes and experienced the greatest reductions in fat intake did show a statistically significant reduction in breast cancer risk (HR 0.78; 95% CI: 0.64-0.95). (38). In the same WHI trial, a low-fat diet was not associated with risk of diabetes (39). However, in WHI observational cohorts higher energy intake was associated with increased risk of some cancers (40) and diabetes (41). The lifestyle factors of diet and physical activity, mediated by BMI, exert overlapping influence on diabetes and cancer, offering opportunities for intervention and treatment, with the goal of reducing risk of both diseases.

Treatment Modalities

As mentioned previously, diabetes treatment modalities have an impact on cancer risk among persons with diabetes. Insulin treatment has been shown to increase the risk of developing solid tumor cancers (17), lung cancer (13) and colorectal adenomas (42). Oral sulfonylureas may lower the risk of cancers, although not as much as metformin (17). The effect of pioglitazone, a type of thiazolidinedione (an agonist of peroxisome proliferator-activated receptors [PPARs]) has been mixed (43), although a 2012 meta-analysis found a significant and positive association between use of pioglitazone and risk of bladder cancer in cohort studies (pooled RR 1.14; 95% CI: 1.04-1.26) (44).

Metformin has demonstrated the greatest potential for reducing cancer risk among persons with diabetes (14-18,45-47), most likely through activation of 5′ adenosine monophosphate-activated protein kinase (AMPK), which reduces glucose production by liver cells; increases insulin sensitivity and fatty acid oxidation; and decreases glucose absorption in the gastrointestinal tract. In a large group of women in the UK, those with diabetes who used more than 40 prescriptions of metformin over more than 5 years had reduced risk of breast cancer when compared with no use of metformin (OR 0.44; 95% CI: 0.24-0.82) (48). Short-term use of metformin was not associated with reduced breast cancer risk (48). Biases can occur in observational studies that may attenuate or exaggerate findings. To test the hypothesis that metformin may reduce cancer risk by one-third, as suggested in observational studies, meta-analysis of nine randomized controlled trials examined cancer incidence and all-cause mortality in adults treated with metformin versus other diabetic treatments (49). Results indicated that treatment with metformin did not lower cancer risk by one-third; RR for cancer incidence in those randomized to metformin compared with placebo, usual, or other active treatments (e.g. a thiazolidinedione) was 1.03; 95% CI: 0.82-1.28 (48). Analysis also failed to show a significant effect of metformin on all-cause mortality (49).

Considerable concern has been expressed about insulin analogs possibly increasing the risk of cancer, particularly breast cancer (17). Changing the chemical structure of insulin through construction of analogs customizes the timing of insulin action by, for example, promoting absorption, slowing release or prolonging binding at the receptor. Glargine, approved for use in 2000 by the United States Food and Drug Administration, is an insulin analog that provides slow-release of insulin with the intent of mimicking basal secretion and levels of insulin. *In vitro* studies suggest that glargine provides up to an eight-fold higher affinity for receptors and high mitogenicity, which can favor cancer development. However, *in vivo*, glargine degrades at the injection site to some degree, which likely attenuates the potential mitogenicity (50).

Concerns surrounding glargine and cancer have resulted in a number of observational studies with mixed results. Some data suggest that glargine does not increase cancer risk (compared with human insulin) (17,51) and other study results suggest that it does (52-53). Examination of adverse events from 31 randomized controlled trials of glargine, using the manufacturer's trials database, concluded that glargine did not increase cancer risk (54), but this conclusion was not universally accepted (55-56).

Randomized controlled trials are considered the "gold standard" of research because randomization should eliminate or minimize biases that can occur with observational studies. In 2003, an international randomized controlled trial of glargine, the Outcomes Reduction with an Initial Glargine Intervention (ORIGIN) (57), began. From 40 countries, a total of 12,612 men and women at risk of cardiovascular disease who had diabetes (88%), or impaired glucose tolerance / impaired fasting glucose (12%), were randomized to receive (1) glargine (plus their current glucose-lowering regimen), (2) standard care (the control group), or (3) omega-3 fatty acids plus their standard care. The hypothesis proposed that glargine or omega-3 fatty acids would reduce the risk of cardiovascular disease. Median follow-up was 6.2 years. Results found similar rates of cardiovascular disease among the glargine and standard care groups (58) and similar incidence among the omega-3 fatty acids and standard care groups (59). Adjudicated outcomes in addition to cardiovascular disease included composite microvascular conditions, incident diabetes, all-cause mortality, and new or recurrent cancers. There was no indication of increased cancer risk in those receiving glargine when compared with standard care. Between the two study assignments, the HR (time-dependent risk) of any cancer was 1.00 with a 95% CI: 0.88-1.13.

(Continued on next page)

Researchers have asked whether the ORIGIN trial results are sufficient to conclude that glargine does not increase cancer risk (60). Pharmacokinetic studies support the ORIGIN trial findings by showing that glargine and its metabolites were rarely found above detectable limits in circulation after subcutaneous injection (61-62). The ORIGIN trial and pharmacokinetic studies strongly suggest the agent is not implicated in increased cancer risk. Further, recently published findings from a four-year French national cohort study investigating glargine and cancer continue to lend evidence that glargine use among persons with diabetes does not increase the risk of cancer (63).

Summary

In the U.S., cancer is the second leading cause of death and diabetes is the seventh (4). Reports of diabetes as a risk factor for cancer began increasing during the 1980s and 1990s, around the same time that rates of overweight and obesity in the U.S. began climbing (64), and obesity was first recognized as a risk factor for cancer (65). All-cause mortality has been found to be higher among persons with cancer who also have diabetes compared with non-diabetic counterparts, although specific cause of death may or may not be cancer. Evidence suggests that maintaining a healthy body weight by balancing energy intake with expenditure and being physically active can decrease the risk of developing cancer among persons with diabetes. Diabetes treatment with metformin and sulfonylureas may decrease the risk of developing cancer, whereas treatment with thiazolidinediones and insulin may increase that risk. Current evidence suggests that glargine does not increase cancer risk.

Registered Dietitians (RDs) have the opportunity and responsibility to counsel clients about the association between cancer and diabetes, and to use this association to motivate clients to attain and maintain a healthy body weight, engage in physical activity, and manage glycosylated hemoglobin levels.

Dr. Tinker is a Nutrition Scientist with the Fred Hutchinson Cancer Research Center in Seattle, WA. Dr. Tinker is also past chair of the Diabetes Care and Education Dietetic Practice Group of the Academy of Nutrition and Dietetics.

References

1. Maynard GD. A statistical study in cancer death-rates. *Biometrika*. 1910;7(3):276-304.
2. Greenwood M, Wood F. The relation between the cancer and diabetes death-rates. *J Hyg (Lond)*. 1914;14(1):83-118.
3. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer.* 2012;107(9):1608-1617.
4. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and Cancer: A consensus report. *Diabetes Care.* 2010;33(7):1674-1685.
5. Luo J, Chlebowski R, Liu S, et al. Diabetes mellitus as a risk factor for gastrointestinal cancers among postmenopausal women. *Cancer Causes Control.* 2013;24(3):577-585.
6. Magliano DJ, Davis WA, Shaw JE, Bruce DG, Davis TM. Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study. *Eur J Endocrinol.* 2012;167(4):589-599.
7. Hartz A, He T, Ross JJ. Risk factors for colon cancer in 150,912 postmenopausal women. *Cancer Causes Control.* 2012;23(10):1599-1605.
8. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. Diabetes and Cause-Specific Mortality in a Prospective Cohort of One Million U.S. Adults. *Diabetes Care.* 2012;35(9):1835-1844.
9. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *The Lancet.* 2008;371(9612):569-578.
10. Duggan C, Irwin ML, Xiao L, et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J Clin Oncology.* 2011;29(1):32-39.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Tumer RC. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
12. Hall GC, Roberts CM, Boulis M, Mo J, MacRae KD. Diabetes and the risk of lung cancer. *Diabetes Care.* 2005;28(3):590-594.
13. Luo J, Chlebowski R, Wactawski-Wende J, Schlecht NF, Tinker L, Margolis KL. Diabetes and Lung Cancer Among Postmenopausal Women. *Diabetes Care.* 2012;24(3):577-585.
14. Monami M, Colombi C, Balzi D, et al. Metformin and Cancer Occurrence in Insulin-Treated Type 2 Diabetic Patients. *Diabetes Care.* 2011;34(1):129-131.
15. Zhang Z-J, Zheng Z-J, Kan H, et al. Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes: a meta-analysis. *Diabetes Care*. 2011;34(10):2323-2328.
16. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care.* 2010;33(2):322-326.
17. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;52(9):1766-1777.
18. Smiechowski BB, Azoulay L, Yin H, Pollak MN, Suissa S. The Use of Metformin and the Incidence of Lung Cancer in Patients With Type 2 Diabetes. *Diabetes Care.* 2012;36(1):124-129.
19. Bodmer M, Becker C, Jick SS, Meier CR. Metformin does not alter the risk of lung cancer: A case-control analysis. *Lung Cancer.* 2012;78(2):133-137.
20. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia*. 2004;47(6):1071-1078.
21. Rodriguez C, Patel AV, Mondul AM, Jacobs EJ, Thun MJ, Calle EE. Diabetes and risk of prostate cancer in a prospective cohort of US men. *Am J Epidemiol.* 2005;161(2):147-152.
22. Weiderpass E, Ye W, Vainio H, Kaaks R, Adami HO. Reduced risk of prostate cancer among patients with diabetes mellitus. *Int J Cancer.* 2002;102(3):258-261.
23. Tseng C-H. Diabetes and Risk of Prostate Cancer: a study using the National Health Insurance. *Diabetes Care.* 2011;34(3):616-621.
24. Andersson B, Marin P, Lissner L, Vermeulen A, Bjorntorp P. Testosterone concentrations in women and men with NIDDM. *Diabetes Care.* 1994;17(5):405-411.
25. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*. 2008;300(23):2754-2764.
26. Currie CJ, Poole CD, Jenkins-Jones S, Gale EAM, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without Type 2 Diabetes. *Diabetes Care.* 2012;35(2):299-304.
27. Landman GW, Van Hateren KJ, Kleefstra N, Bilo HJ. The relationship between obesity and cancer mortality in type 2 diabetes: a ten-year follow-up study (ZODIAC-21). *Anticancer Research.* 2010;30(2):681-682.
28. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncology.* 2011;29(1):40-46.

29. Ewertz M, Jensen M-B, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncology.* 2011;29(1):25-31.
30. Cohen DH, Leroith D. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. *Endocrine-Related Cancer*. 2012;19(5):F27-F45.
31. Green LE, Dinh TA, Smith RA. An estrogen model: the relatiopnship between body mass index, menopausal status, estrogen replacement therapy, and breast cancer risk. *Comput Math Methods Med*. 2012; 2012;792375. doi:10.1155/2012/792375.
32. Cleary MP, Grossmann ME. Obesity and breast cancer: the estrogen connection. *Endocrinology*. 2009;150(6):2537-2542.
33. Maccio A, Madeddu C. Obesity, inflammation, and postmenopausal breast cancer: therapeutic implications. *Scientific World Journal.* 2011;11:2020-2036.
34. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective*. Washington DC; 2007. http://www.dietandcancerreport.org/global_network/global_network_vision.php. Accessed May 14, 2013.
35. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA*. 2001;286(8):921-929.
36. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219-229.
37. Montonen J, Boeing H, Fritsche A, et al. Consumption of red meat and whole-grain bread in relation to biomarkers of obesity, inflammation, glucose metabolism and oxidative stress. *Eur J Nutr.* 2012;52(1):337-345.
38. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):629-642.
39. Tinker LF, Bonds DE, Margolis KL, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. *Arch Intern Med.* 2008;168(14):1500-1511.
40. Prentice RL, Shaw PA, Bingham SA, et al. Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. *Am J Epidemiol.* 2009;169(8):977-989.
41. Tinker LF, Sarto GE, Howard BV, et al. Biomarker-calibrated dietary energy and protein intake associations with diabetes risk among postmenopausal women from the Women's Health Initiative. *Am J Clin Nutr.* 2011;94(6):1600-1606.
42. Wong P, Weiner MG, Hwang WT, Yang YX. Insulin therapy and colorectal adenomas in patients with diabetes mellitus. *Cancer Epidemiol Biomarkers* 2012;21(10):1833-1840.
43. Ferrara A, Lewis JD, Quesenberry CP, et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care.* 2011;34(4):923-929.
44. Kermode-Scott B, Clyne M. Meta-analysis confirms raised risk of bladder cancer from pioglitazone. BMJ. 2012;345:e4541.
45. Ruiter R, Visser LE, van Herk-Sukel MPP, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. *Diabetes Care.* 2012;35(1):119-124.
46. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care.* 2009;32(9):1620-1625.
47. Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. Diabetes, metformin, and breast cancer in postmenopausal women. *J Clin Oncology*. 2012;30(23):2844-2852.
48. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care*. 2010;33(6):1304-1308.
49. Stevens RJ, Ali R, Bankhead CR, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia*. 2012;55(10):2593-2603.
50. Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia*. 2009;52(9):1699-1708.
51. Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia*. 2009;52(9):1755-1765.
52. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies - a population-based follow-up study in Sweden. *Diabetologia*. 2009;52(9):1745-1754.
53. Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia*. 2009;52(9):1732-1744.
54. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia*. 2009;52(12):2499-2506.
55. Hemkens LG, Grouven U, Bender R, Sawicki PT. Insufficient evaluation of adverse events is not a proof of safety. *Diabetologia*. 2010;53(4):790-792.
56. Home PD, Lagarenne P. Insufficient evaluation of adverse events is not a proof of safety. Reply to LG Hemkens, U Grouven, R Bender, et al. [letter]. *Diabetologia*. 2010;53(4):793-794.
57. The ORIGIN Trial Investigators: Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dystlycemia: The ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). *Am Heart Journal.* 2008;155(1):26-32.
58. The ORIGIN Trial Investigators; Gerstein HC, Bosch J, Dagenais GR, et al. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. *New Engl J Med.* 2012;367(4):319-328.
59. The ORIGIN Trial Investigators; Bosch J, Gerstein HC, Dagenais GR, et al. n–3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia. *New Engl J Med*. 2012;367(4):309-318.
60. Owens DR. Glargine and Cancer: Can We Now Suggest Closure? *Diabetes Care*. 2012;35(12):2426-2428.
61. Bolli GB, Hahn AD, Schmidt R, et al. Plasma Exposure to Insulin Glargine and Its Metabolites M1 and M2 After Subcutaneous Injection of Therapeutic and Supratherapeutic Doses of Glargine in Subjects With Type 1 Diabetes. *Diabetes Care*. 2012;35(12):2626-2630.
62. Lucidi P, Porcellati F, Rossetti P, et al. Metabolism of Insulin Glargine After Repeated Daily Subcutaneous Injections in Subjects With Type 2 Diabetes. *Diabetes Care.* 2012;35(12):2647-2649.
63. Fagot J-P, Blotière P-O, Ricordeau P, Weill A, Alla F, Allemand H. Does Insulin Glargine Increase the Risk of Cancer Compared With Other Basal Insulins?: A French nationwide cohort study based on national administrative databases. *Diabetes Care.* 2013;36(2):294-301.
64. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the united states, 1991-1998. *JAMA*. 1999;282(16):1519-1522.
65. Katzmarzyk PT, Reeder BA, Elliott S, Joffres MR, Pahwa P, Raine KD, et al. Body mass index and risk of cardiovascular disease, cancer and all-cause mortality. *Can J Public Health*. 2012;103(2):147-151.

After reading this issue of *On the Cutting Edge* and the *Oncology Nutrition Connection*, "Diabetes and Cancer: Addressing Interrelationships and Treatment Recommendations," DCE and ON members can earn 3.0 hours of free continuing professional education units (CPEUs level ll) approved by the Commission on Dietetic Registration (CDR). CPE eligibility is based on active DCE/ON membership status from June 1, 2012 to May 31, 2013.

For DCE members, read the entire issue, complete the post-test on the CPEUs page on the DCE website, by May 31, 2014; http://www.dce.org/resources/cpeus. For each question, select the one best response. After passing the quiz, to view/print your certificate, access your CPEU credit history or view the learning objectives, go to http://www.dce.org/account/history.

For ON members, read the entire issue, answer the CPE test questions and compare your answers to the answer key posted in the newsletter. Credit is awarded to the RDs who correctly answer eight of the questions. Log onto the ON website, newsletter section, to access and print the CPE certificate.

You are responsible to record 3.0 hours on your Learning Activities log and retain the certificate of completion in the event you are audited by CDR. The certificate of completion is valid when the CPE questionnaire is successfully completed, submitted to and record by DCE/Academy of Nutrition and Dietetics.

Diabetes and Cancer CPE Questions- Spring 2013

1. **Which of the following supplements may improve insulin secretion/sensitivity?**
   a. Allyl sulfides and ginseng
   b. Curcumin and magnesium
   c. Ginseng and magnesium
   d. Allyl sulfides and curcumin

2. **How much more frequently do individuals with type 2 diabetes use non-mineral/non-vitamin supplements compared to individuals with type 1 diabetes?**
   a. Usage is the same in both populations
   b. 1.5 times
   c. 2 times
   d. 3 times

3. **Based on National Health and Nutrition Examination Survey (NHANES) data from 2003-2004, the major source of added sugars for children appears to be:**
   a. Candy
   b. Cookies/cakes
   c. Sweetened cereals
   d. Sweetened beverages/drinks

4. **In overweight and obese individuals, the overproduction of leptin:**
   a. Signals appetite reduction to the brain
   b. Leads to increased appetite and energy intake
   c. Is not associated with consumption of high-fructose corn syrup
   d. Has no association with increased adiposity

5. **According to the Academy of Nutrition and Dietetics Evidence Analysis Library, what level of sucrose intake, expressed as a percentage of total calories, does NOT have a negative impact on glycemic response when substituted for isocaloric amounts of starch?**
   a. 5%-10%
   b. 10%-35%
   c. 35%-45%
   d. 45%-50%

6. **What minimum level of total carbohydrate consumption do experts recommend to provide adequate glucose to fuel the central nervous system?**
   a. 100 g
   b. 120 g
   c. 130 g
   d. 140 g

7. **The American Cancer Society recommends that individuals who are overweight or obese work toward an initial weight loss goal of:**
   a. 1%-3%
   b. 3%-5%
   c. 5%-7%
   d. 7%-9%

8. **The American Cancer Society and American Diabetes Association guidelines for prevention of both cancer and diabetes include:**
   a. Avoidance of alcohol
   b. High protein consumption
   c. Intensive physical activity
   d. Limited intake of sugary drinks

9. **Which of the following statements regarding the relationship of obesity with cancer and diabetes is correct?**
   a. Obesity increases the risk of developing both cancer and diabetes
   b. Obesity increases the risk of developing diabetes, but not cancer
   c. Obesity is not associated with developing cancer
   d. Risk factors for developing diabetes and cancer are not related

10. **According to the American Institute for Cancer Research, approximately what percentage of overall cancer diagnoses may be prevented by healthy patterns of diet and physical activity?**
    a. 10%
    b. 25%
    c. 30%
    d. 50%

The "Sweet" Truth About Cancer

Niyati Parekh, PhD, RD

Abstract

Over the past three decades there has been a dramatic increase in the consumption of added sugars in the United States (U.S.). This increase parallels the rapid growth of the processed food industry and increased prevalence of obesity. For most Americans, consumption of added sugars from foods and beverages exceed the recommendations for sugar intake based on the 2010 Dietary Guidelines for Americans (1). Clear and consistent associations have been observed between increased intakes of sugar sources, obesity, related cardiometabolic diseases (2) and colorectal cancer (3). Herein we discuss the major food sources of added sugars, potential biologic mechanisms that link sugar intake to cancer, existing evidence in human studies that explore the sugar-cancer connection, and clinical implications for patients and health care providers.

Major Sources of Sugars in the U.S.

Total dietary sugars include "intrinsic" or natural sugars present in foods, as well as "extrinsic" or added sugars. Natural sugars, such as fructose and lactose, are found in whole fruit, vegetables, and milk products, which also provide nutrients and phytochemicals that are beneficial to one's health. On the other hand, extrinsic sugars are caloric sweeteners that have been added to foods or beverages during processing or preparation, and are also consumed separately at the table. These foods tend to be calorie-dense and lack essential nutrients. Examples of added sugars are sucrose (table sugar), high-fructose corn syrup (HFCS), honey, molasses, and syrups. High-fructose corn syrup is the predominant sweetener in soft drinks in the U.S., and a major source of dietary sugars, representing 75% of corn-based sweeteners and 40% of total caloric sweeteners consumed in America (4). Surprisingly, sugar is a major food additive in savory foods as well, including breads, pizzas, and pasta sauces (4).

The top contributors of overall carbohydrate intake and sugar intake in the U.S. have varied over the years, in parallel with changes in the U.S. food supply. Based on dietary intake data from the Continuing Survey of Food Intakes by Individuals (CSFII) from 1981 to 1991, the top sources of dietary carbohydrates in the diets of Americans were yeast bread, soft drinks or soda, cakes, cookies, quick breads, doughnuts, sugars, syrups, and jams, potatoes, ready-to-eat cereal, and pasta (5), many of which are also top sources of added sugar. Data from the 1994-1996 CSFII cycle indicated that Americans consumed around 82 g/day of carbohydrates from added sugars, which contributed around 16% of total energy intake (6). The major source of these sugars was soft drinks, which account for about one third of total added sugar intake. Other sources included table sugar, syrup, sweets, sweetened drinks, regular "fruit-ades" and drinks, and flavored milk products. More recently, the National Health and Nutrition Examination Survey (NHANES) data from 2003-2004 indicate that the top sources of added sugars are soda, fruit drinks, grain desserts, dairy desserts, candy, and cold cereals. For children, the top source of added sugars is sugar-sweetened beverages (7). In fact, Americans consume 200-300 more calories daily compared to 30 years ago, primarily due to the increase in the consumption of sugary drinks (8). Figure 1 from 2005-2006 NHANES data outlines sources of added sugars in U.S. diets (1,9).

Overview of Sugar Metabolism

The body uses sugar for energy, regardless of whether it is natural or processed. Digestion of all carbohydrates, including sugar, begins in the mouth under the action of lingual amylase (10). Digestion into monosaccharides (glucose, fructose, galactose) and disaccharides (sucrose, maltose) continues in the stomach under the action of pancreatic amylase and ends in the intestine. The resulting products of digestion, primarily glucose, are then absorbed and transported to the liver (10). After glucose is absorbed, it has three potential fates through six possible pathways. Glucose is either oxidized for energy via glycolysis and the Kreb's cycle by body tissues; stored in the liver and the muscles as glycogen; or converted into other carbohydrates such as fructose (10).

In individuals with excessive sugar intakes, the conversion of glucose into other carbohydrates such as fructose via the polyol pathway and to glucosamine via the hexosamine pathway is elevated, resulting in increased advanced glycation products (AGE) formation and consequently increased markers of oxidative stress, all of which are involved in cancer growth and metastasis (10-11). In addition, there is evidence that fructose is metabolized differently from glucose (10). Fructose lowers insulin secretion compared to glucose-containing carbohydrates, leading to lower circulating leptin concentrations; leptin secretion is regulated by insulin. Leptin plays an important role in energy balance and appetite control; it typically signals appetite reduction in the brain among lean individuals (12). However, in overweight and obese individuals, overproduction of leptin can lead to "leptin resistance" in the brain, leading to increased appetite and energy intake. Because of these hormonal effects, diets high in fructose may increase the likelihood of weight gain and its associated metabolic sequelae such as insulin

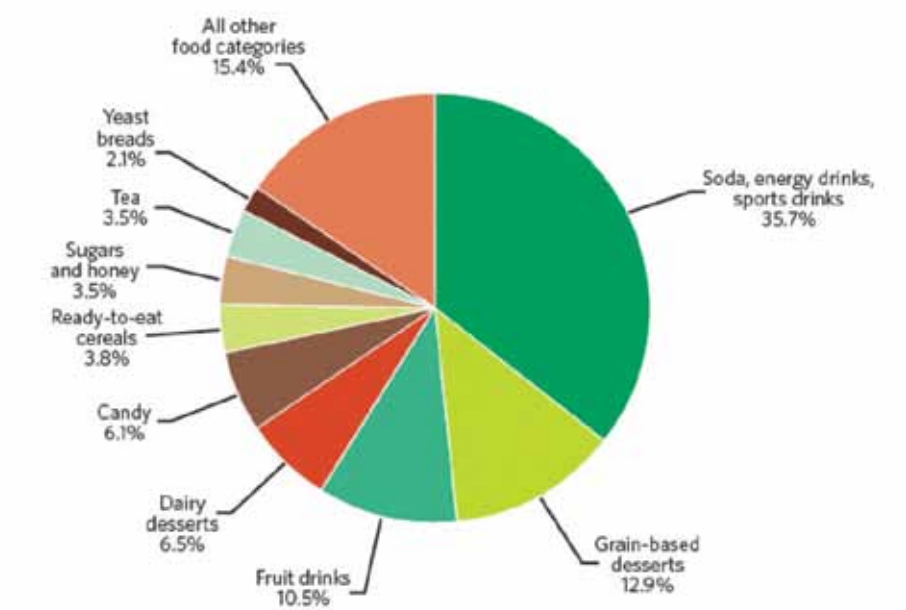
(Continued on next page)

resistance (13). In addition, fructose, when compared with glucose, is preferentially metabolized to lipid in the liver (13), therefore high fructose intakes are associated with dyslipidemia, increased adiposity, and decreased insulin sensitivity (14). Glucose and fructose are usually not consumed in isolation. In fact, similar to sucrose, high fructose corn syrup is composed of both glucose and fructose. High fructose corn syrup is a key source of sugar in the American diet and the evidence is equivocal about its role in obesity and related health outcomes (15).

Dietary Guidelines for Sugar Intake

The 2010 Dietary Guidelines for Americans recommend limiting calories from added sugars to 5%-15% of total energy intake; however consumption of added sugars in the U.S. exceeds these recommendations (1,16). On the other hand, the American Heart Association has published more specific guidelines for added sugar, recommending that women consume no more than 100 calories per day from added sugars and that men consume no more than 150 calories per day from added sugars (17). This is equivalent to a maximum of 6 teaspoons of added sugar daily for women and 9 for men. The American Cancer Society (ACS) also recommends limiting the intake of sugar and sweetened beverages such as soft drinks, sport drinks, and fruit flavored drinks (18). Limiting consumption of refined carbohydrate foods, such as pastries, candy, sugar sweetened breakfast cereal and other high sugar food is emphasized as well. Lastly, ACS recommends choosing whole grain bread, pasta, cereal (such as barley and oats) and brown rice instead of refined grains. The American Institute for Cancer Research (AICR) (3-19) recommends limiting refined sugar consumption to less than 10% of total energy intake, and avoiding syrups such as those found in soft drinks, which typically contain high amounts of sugar. Additionally, AICR recommends limiting refined carbohydrates and instead consuming approximately 600-800 g (20-30 ounces) or ≥ 7 portions per day of unprocessed carbohydrates, such as cereal grains, legumes, roots, tubers and plantains. AICR also recommends consuming a diet rich in vegetables and fruits, which provides approximately 5 portions per day (3 portions of vegetables and 2 portions of fruits) of these foods in total. The table summarizes recommendations for sugar intake for these organizations.

FIGURE 1. Sources of Added Sugars in the Diets of the U.S. Population Ages 2 Years and Older, NHANES 2005-2006[a]



a. Data are drawn from analyses of usual dietary intake conducted by the National Cancer Institute. Foods and beverages consumed were divided into 97 categories and ranked according to added sugars contribution to the diet. "All other food categories" represents food categories that each contributes less than 2% of the total added sugar intake.

Source: National Cancer Institute. Sources of added sugars in the diets of the U.S. population ages 2 years and older, NHANES 2005-2006. Risk Factor Monitoring and Methods. Cancer Control and Population Sciences. http://riskfactor.cancer.gov/diet/foodsources/added_sugars/table5a.html. Accessed August 11, 2010.

Table. Sugar Intake Recommendations

Organization	Sugar Intake Recommendations
2010 Dietary Guidelines for Americans (DGA)	Limit calories from added sugars to 5%-15% of total energy intake (1).
American Heart Association (AHA)	Women: Consume no more than 100 calories per day from added sugars (17). Men: Consume no more than 150 calories per day from added sugars (17).
American Cancer Society (ACS)	Limit intake of sugar and sweetened beverages such as soft drinks, sport drinks, and fruit flavored drinks (18). Limit intake of refined carbohydrate foods such as pastries, candy, sugar sweetened breakfast cereal and other high sugar food (18).
American Institute for Cancer Research (AICR)	Limit refined sugar intake to less than 10% of total energy intake (3,19). Avoid syrups such as those found in soft drinks, which typically contain high amounts of sugar.

High Sugar Diets, Insulin, Glucose Metabolism and Cancer

The evidence on an association between diets high in sugars and cancer incidence is observational, and cannot prove cause and effect, though data suggest a connection (20). A prospective cohort study among

Swedish women suggests that breast cancer risk is significantly higher among women who consume a high glycemic load (GL) diet (20). A significantly higher risk of gastric and colorectal cancers also have been observed with a high GL diet (21-23). Intake of high-fiber foods that are often classified as low GL foods is associated with a lower risk of gastrointestinal cancers (24-25). The World Cancer Research Fund (WCRF)/AICR expert panel concluded that sugar is a risk factor for colon cancer based on the limited available evidence (3-19). WCRF/AICR evidence also suggests that Western diets, high in sugars and refined carbohydrates, are associated with increased breast and colon cancer risk (3-19).

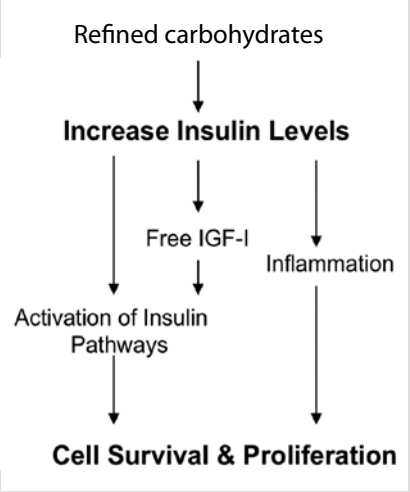
Potential underlying mechanisms through which sugars are thought to influence cancer risk involve metabolic alterations in insulin (26). Associations are more robust for studies examining blood glucose concentrations and cancer risk. Three large prospective cohort studies in Austrian, Swedish, and Korean populations noted a 20%-31% increased overall cancer risk among those with elevated blood glucose concentrations (27-29). Additionally, a study by Parekh et al. (30) documented an increased risk of cancer mortality among people with insulin resistance. A meta-analysis of prospective studies suggested a modest increased risk of colon and pancreatic cancer in persons with perturbations in the insulin-glucose axis (31). An unpublished study by Parekh et al. noted that impaired fasting glucose was associated with a greater than 2-fold increased risk of colorectal cancer and overall obesity-related cancer risk in the prospective Framingham Heart Study. However, it must be noted that associations in the literature vary depending on the study design and biomarkers used. For example, in prospective studies examining breast cancer risk, one noted a significant increased risk with elevated glucose (29), while others noted null associations (27,32-33), but did note associations with insulin (32-33) or diabetes status (27).

Potential Biological Links Between Sugar and Cancer

Diets high in sugar have been hypothesized to influence cancer through increased adiposity, oxidative stress, and by increasing insulin and insulin-like growth factor-1 levels (34). Furthermore, sugars may directly serve as "fuel" for the altered metabolism of cancer cells, which have a high demand for glucose, as they more rapidly enter the anaerobic glycolytic pathway compared with normal cells (35-36). Higher blood glucose concentrations lead to higher body insulin concentrations. Insulin is a metabolic signal that serves as a communicator of nutritional state, and influences carcinogenesis through its ability to support cell differentiation and survival. Insulin increases the production of free insulin-like growth factor-1 (IGF-1), a mitogenic agent, and adipocyte-derived vascular endothelial growth factor (VEGF), a critical proangiogenic factor, which influences cell survival and migration (37). Hyperinsulinemia also promotes inflammation, which is an established factor in carcinogenesis (38). Furthermore, glucose up-regulates cell growth by activating cell proliferation factors, and delays apoptosis (35). Figure 2 outlines the proposed mechanisms through which sugar may influence cancer risk.

A key mechanism through which insulin may increase cancer risk is by activation of target genes downstream of the insulin receptor (i.e., post-receptor effect), which comprise a signaling network that dictates cell growth, survival and proliferation (38-39). The insulin-signaling pathway determines cell fate (e.g., proliferation, protein synthesis, angiogenesis, or apoptosis). Dysregulation of the insulin-signaling pathway has been demonstrated in numerous cancers including those of the breast, prostate, colon, and uterus (40). Evidence has shown that variants in the IRS-1 gene, a gene in the insulin-signaling pathway, increased risk by approximately 3-fold for breast (41) and 1.4-fold for colon cancer in a population-based U.S. study (42). Similarly, IRS-2 polymorphisms have also been associated with colorectal cancer

FIGURE 2. Potential Mechanisms Linking Sugar with Cancer



risk (42). Multiple studies have investigated polymorphisms in the IGF-1 gene and its receptor (IGF-1R) (43-46). The mTOR gene is a key gene in the insulin-signaling pathway, which controls cell proliferation in response to growth factors or nutrients, and may cause aberrant activation of downstream genes including Akt, eIF4E, 4E-BP1 and p70SK6 (47-48). Together, these perturbations enhance cell growth, survival and migration (47), and may adversely influence circulating levels of insulin, thereby perpetuating its action (49). Modifiable lifestyle factors such as diet and physical activity may alter expression of genes in the insulin-signaling pathway, suggesting that the examination of the combined impact of dietary and genetic factors is worthy of investigation in future studies.

One determinant of circulating insulin concentrations is diet, specifically carbohydrate intake (50). Diets high in refined carbohydrates and sugars can cause a quick rise in blood glucose and stimulate insulin secretion into the blood. In contrast, diets high in fiber may impede quick absorption of glucose into the bloodstream, blunt the insulin response, and promote more favorable insulin profiles (51). Two commonly used measures of the degree to which foods may raise blood glucose concentrations are (1) Glycemic index (GI)

(Continued on next page)

and (2) Glycemic Load (GL). GI is defined as the average blood glucose response of foods as compared to a white bread standard or glucose (52). In comparison, GL is a measure of the glycemic effect of the total diet and it combines both the GI of a food and its portion size (53). Evidence from the Framingham Heart Study (FHS) (54) and other populations (55) suggest that high GI and GL diets negatively impact overall glycemic profiles. As previously stated, the link between cancer and refined carbohydrates, specifically sugar intake, may lie in the fact that insulin, released in response to carbohydrate intake, is an important cell growth and mitotic factor. Reducing the glycemic effect of the diet may simultaneously influence adiposity, its underlying metabolic disturbances, activity of the "nutrient-sensing" signaling pathways, and possibly cancer (48). The WCRF/AICR report claims that altering diet may play a central role in reducing worldwide cancer incidence (3), which underscores the importance of further investigation into these relationships in human populations to clarify the hypothesized associations between higher sugar intake and increased cancer risk.

Practical Implications for Patients:

- Limit sugars and refined grains in order to reduce the risk of some cancers. Some examples of refined grains are white bread, regular refined pasta, white rice and white flour. Whole grains include brown rice, quinoa, whole-wheat pasta, whole-wheat flour, whole-wheat bread and barley.
- Reduce or eliminate intake of sugary drinks. Decrease the number and quantity of drinks per day or replace them with non-sugary drinks such as sparkling water combined with small amounts of fruit juice, non-caloric sodas, tea, coffee and plain water.
- Decrease the consumption of sugary foods such as chocolate bars, cakes, cookies, cupcakes, and candy by eating these foods less often and reducing portion sizes.
- Consume natural sweets such as fruits because they are nutrient-dense, containing numerous vitamins, minerals, and phytochemicals. The antioxidants and phytochemicals provided by fruit are hypothesized to reduce cancer risk as well.
- Read ingredient lists and nutrition labels, and be aware that sugar can be "hidden" under different names. The ingredients on the nutritional label are listed in descending order, with the ingredient present in the largest quantities listed first. If sugar is the first ingredient on the list, then the product has a lot of added sugar.

Niyati Parekh, PhD, RD, is Assistant Professor of Nutrition and Public Health, Department of Nutrition, Food Studies and Public Health, Steinhardt School and Department of Population Health, Langone School of Medicine. New York University, New York, New York

ACKNOWLEDGEMENTS:

Dr. Parekh would like to acknowledge Nour Makarem, MS, RD, Department of Nutrition, Food Studies and Public Health and Ina Flores, MS, RD, Senior Dietitian at the Mount Sinai School of Medicine, for their research assistance.

References

1. U.S. Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2010*. 7th Edition. Washington, DC: US Government Printing Office, December 2010.
2. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010 Nov;33(11):2477-2483.
3. World Cancer Research Fund/ American Institute for Cancer Research. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective.* Washington D.C.; 2007.
4. United States Department of Agriculture Chapter 2: Profiling Food Consumption in America. *Agriculture Fact Book*. Washington, DC: US Government Printing Office; 2001-2002. P. 12-21.
5. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. *J Am Diet Assoc.* 1998.98(5):537-547.
6. Guthrie JF and Morton JF. Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc.* 2000;100(1):43-51.
7. Reedy J and Krebs-Smith SM. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. *J Am Diet Assoc.* 2010;110(10):1477-1484.
8. New York City Department of Health and Mental Hygiene. Physical Activity and Nutrition: Sugary Drinks. 2012. Available from: http://www.nyc.gov/html/doh/html/cdp/cdp_pan_pop.shtml. Accessed November 5, 2012.
9. U.S. Department of Agriculture. USDA Database for the Added Sugar Content of Selected Foods. 2006. Available from: http://www.nal.usda.gov/fnic/foodcomp/Data/add_sug/addsug01.pdf. Accessed November 22, 2012.
10. Keim NL, Levin RJ, Havel PJ. Carbohydrates. In Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, eds. *Modern Nutrition in Health and Disease.* 10th ed. Baltimore, MD: Philadelphia: Lippincott Williams & Wilkins; 2006: 62-82.
11. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc.* 2010;110(6):911-916.
12. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. *J Clin Endocrinol Metab.* 2004;89(2):447-452.
13. Elliott SS, Keim NL, Stern JS, Teff K Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr.* 2002;76(5):911-922.
14. Stanhope KL, Schwarz JM, Keim ML Griffen SC Bremer AA, Graham JL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest.* 2009;119(5):1322-1334.
15. Rippe JM, Angelopoulos TJ. Sucrose, high-fructose corn syrup, and fructose, their metabolism and potential health effects: what do we really know? *Adv Nutr.* 2013;4:236-245. doi: 10.3945/an.112.002824.
16. Welsh JA, Sharma AJ, Grellinger L, Vos MB. Consumption of added sugars is decreasing in the United States. *Am J Clin Nutr.* 2011;94:(3):726-734.
17. American Heart Association. Sugars and Carbohydrates. 2012. Available from: http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyDietGoals/Sugars-and-Carbohydrates_UCM_303296_Article.jsp. Accessed on: November 30, 2012.
18. American Cancer Society. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention. 2012. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/002577-pdf.pdf. Accessed on: February 24, 2013.

19. The American Institute for Cancer Research. AICR Guidelines for Cancer Prevention: 2012. http://www.aicr.org/publications/aicr/pub_aicr_guidelines.html. Accessed November 30, 2012.
20. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. *Int J Cancer.* 2009;125(1):153-157.
21. Bertuccio P, Praud D, Chatenoud L, Lucenteforte E, Bosetti C, Pelucchi C, et al. Dietary glycemic load and gastric cancer risk in Italy. *Br J Cancer.* 2009;100(3):558-561.
22. Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005;14(1):138-147.
23. Higginbotham S, Zhang ZF, Lee IM, Cook NR, Giovannucci E, Buring JE, et al. Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst.* 2004;96(3):229-233.
24. Gonzalez CA, Riboli E. Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Cancer.* 2010;46(14):2555-2562.
25. Egeberg R, Olsen A, Loft S, Christensen J, Johnsen NF, Overvad K, et al. Intake of wholegrain products and risk of colorectal cancers in the Diet, Cancer and Health cohort study. *Br J Cancer.* 2010;103(5):730-734.
26. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Archives of Physiology and Biochemistry.* 2008;114(1):71-83.
27. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA.* 2005;293(2):194-202.
28. Stattin P, Bjor O, Ferrari P, Lukanova A, Lenner P, Lindahl B, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care.* 2007;30(3):561-567.
29. Rapp K, Schroeder J, Klenk J, Ulmer H, Concin H, Diem G, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia.* 2006;49(5):945-952.
30. Parekh N LY, Hayes RB, Albu JB, Lu-Yao GL. Longitudinal associations of blood markers of insulin and glucose metabolism and cancer mortality in the third National Health and Nutrition Examination Survey. *Cancer Causes Control.* 2010;21(4):631-642.
31. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. *Archives of Physiology and Biochemistry.* 2008;114(1):63-70.
32. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009;101(1):48-60.
33. Kabat GC, Kim M, Caan BJ, Chlebowski RT, Gunter MJ, Ho GY, et al. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer. 2009;125(11):2704-2710.
34. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Archives Physiol Biochem.* 2008;114(1):71-83.
35. Ganapathy V, Thangaraju M, Prasad PD. Nutrient transporters in cancer: relevance to Warburg hypothesis and beyond. *Pharmacol Ther.* 2009;121(1):29-40.
36. Vander Heiden MG PD, Rathmell JC, Fox CJ, Harris MH, Thompson CB. Growth factors can influence cell growth and survival through effects on glucose metabolism. *Mol Cell Biol.* 2001;21(17):5899-5912.
37. Hausman GJ, Richardson RL. Adipose tissue angiogenesis. *J Anim Sci.* 2004;82(3):925-934.
38. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med.* 2010;61:301-316.
39. Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol.* 2009;27(13):2278-2287.
40. LoPiccolo J, Blumenthal GM, Bernstein WB, Dennis PA. Targeting the PI3K/Akt/mTOR pathway: effective combinations and clinical considerations. *Drug Resist Updat.* 2008;11(1-2):32-50.
41. Slattery ML, Sweeney C, Wolff R, Herrick J, Baumgartner K, Giuliano A, et al. Genetic variation in IGF1, IGFBP3, IRS1, IRS2 and risk of breast cancer in women living in Southwestern United States. *Breast Cancer Res Treat.* 2007;104(2):197-209.
42. Slattery ML, Samowitz W, Curtin K, Ma KN, Hoffman M, Caan B, et al. Associations among IRS1, IRS2, IGF1, and IGFBP3 genetic polymorphisms and colorectal cancer. *Cancer Epidemiol Biomarkers Prev.* 2004;13(7):1206-1214.
43. Gu F, Schumacher FR, Canzian F, Allen NE, Albanes D, Berg CD, et al. Eighteen Insulin-like Growth Factor (IGF) pathway genes, circulating levels of IGF-1 and its binding protein (IGFBP-3), and risk of prostate and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19(11):2877-2887.
44. Canzian F, McKay JD, Cleveland RJ, Dossus L, Biessy C, Rinaldi S, et al. Polymorphisms of genes coding for insulin-like growth factor 1 and its major binding proteins, circulating levels of IGF-I and IGFBP-3 and breast cancer risk: results from the EPIC study. *Br J Cancer.* 2006;94(2):299-307.
45. Canzian F, Cox DG, Setiawan VW, Stram DO, Ziegler RG, Dossus L, et al. Comprehensive analysis of common genetic variation in 61 genes related to steroid hormone and insulin-like growth factor-I metabolism and breast cancer risk in the NCI breast and prostate cancer cohort consortium. *Hum Mol Genet.* 2010;19(19):3873-3784.
46. Park K, Kim JH, Jeon HG, Byun SS, Lee E. Influence of IGFBP3 gene polymorphisms on IGFBP3 serum levels and the risk of prostate cancer in low-risk Korean men. *Urology.* 2010;75(6):1516 e1-7.
47. Ghayad SE, Cohen PA. Inhibitors of the PI3K/Akt/mTOR Pathway: New Hope for Breast Cancer Patients. Recent Pat Anticancer Drug Discov. 2010;5(1):29-57.
48. Hursting SD, Lashinger LM, Wheatley KW, Rogers CJ, Colbert LH, Nunez NP, et al. Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link. Best Pract Res Clin Endocrinol Metab. 2008;22(4):659-669.
49. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proenca C, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. *Nat Genet.* 2009;41(10):1110-1115.
50. Liese AD, Schulz M, Fang F, Wolever TMS, D'Agostino RB, Sparks KC, et al. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 2005;28(12):2832-2838.
51. Priebe MG, van Binsbergen JJ, de Vos R, Vonk RJ. Whole grain foods for the prevention of type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2008(1):CD006061.
52. Wolever TM, Nguyen PM, Chiasson JL, Hunt JA, Josse RG, Palmason C, et al. Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr.* 1994;59(6):1265-1269.
53. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr.* 2002;76(1):5-56.
54. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care.* 2004;27(2):538-546.
55. Burton-Freeman BM, Keim NL. Glycemic index, cholecystokinin, satiety and disinhibition: is there an unappreciated paradox for overweight women? *Int J Obes* (Lond). 2008;32(11):1647-1654.

Use of Herbal, Botanical and Natural Product Supplements in Oncology and Diabetes Populations

Caitlin Dow, PhD and Maureen Leser, MS, RD, CSO, LD

Abstract

It is well recognized that herbal and botanical products exert biologic effects. Over 50% of commercial drugs are derived from bioactive compounds of non-human origin, many of which are plants (1). As increasing numbers of Americans have become disillusioned with perceived over-use, adverse side effects, and high cost of prescription drugs, they have turned to herbal and botanical supplements, which many consider natural and safer than synthetic medications (2). A new medical diagnosis also can stimulate lifestyle changes, including an increase in the use of dietary supplements (3).

Dietary supplement use, particularly multivitamins, is highly prevalent in the United States. Use is reportedly higher in older, female, overweight/obese individuals as well as those with health concerns. Data from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) indicate that approximately 54% of adults (excluding pregnant women) and 70% of adults >71 years of age take multi-vitamin and mineral supplements, while 20% of Americans use a supplement with at least one botanical ingredient (4). A survey published in 2008 by the National Center for Complementary and Alternative Medicine (NCCAM) indicated that herbal therapy or use of natural products other than vitamins and minerals was the second most prevalent alternative medicine modality (excluding prayer), and used by 18.9% of adults (5). Individuals with chronic disease, including cancer and diabetes mellitus, frequently supplement their diets with herbal and natural therapies, possibly due to real or perceived limitations of conventional treatments (6).

The evidence base for herbal/dietary supplements used to prevent or improve therapeutic outcomes in diabetes and cancer remains limited, and concern over potential harm remains (6-7). Because of the widespread use of these products, it is important for the registered dietitian (RD) to understand and recognize potential benefits, as well as potential adverse events associated with supplementation. This paper briefly reviews usage of supplements in oncology and diabetes patients; potential biological benefits and risks of select supplements used by each population; the current legislative framework for dietary supplements; and the role of the RD in counseling patients on supplement usage.

Chronic Disease and Dietary Supplements

Adults with cancer or other chronic conditions are more likely to report use of supplements than healthy populations (8). Supplement usage is widespread amongst oncology patients, and data indicate that usage typically ranges from 30-75% in this population (9). One pilot study of 140 oncology patients indicated that 52% were taking some kind of dietary supplements and, of those, 23% were using herbal supplements. Factors associated with herbal supplement use were female gender, age, fatigue, cancer pain, and presence of metastasis (7). A subset of participants enrolled in the American Cancer Society's Study of Cancer Survivors-I (SCS-I) self-administered a dietary supplement survey. Of 827 surveys included in the review, approximately 97% of participants had undergone conventional therapy for their cancer, yet 69.3% also reported using dietary supplements after their cancer diagnosis. Garlic, echinacea, ginseng, black cohosh, and gingko biloba were included in the list of supplements (other than multivitamins) taken by 10 or more people in this study (10).

Similar to patients diagnosed with cancer, supplementation with herbal/dietary agents is common in people diagnosed with diabetes. Those with diabetes often report use of dietary supplements and other alternative medicines because of a desire to take an active role in their health; to improve their quality of life; or due to a belief that conventional therapies do not work or are too expensive (11). Data from the 2002 and 2007 National Health Interview Study found that of 4,150 individuals diagnosed with Type 1 or Type 2 Diabetes, approximately 34% were taking at least one non-vitamin/non-mineral dietary supplement (11). A recent retrospective study in 459 adults with diabetes indicated that 55% used some form of vitamin, mineral, or herbal supplement on a daily basis (12). Interestingly, the use of non-mineral/non-vitamin supplements was twice as common among type 2 diabetics as compared to type 1 diabetics (39% vs. 20%, respectively) (12). Among the more frequently consumed dietary supplements were cinnamon, coenzyme Q10, chromium, and alpha-lipoic acid.

Target Mechanisms for Diet Supplementation in Cancer and Diabetes

The use of dietary supplements is often driven by an assumption that such products may modify health by targeting the specific pathology associated with disease. For cancer patients and/or those with a diagnosis of diabetes this may include modulation of inflammation, oxidative stress, insulin resistance, and/or hyperglycemia. Evidence exists to suggest that some compounds do favorably alter these biological responses. Curcumin may reduce inflammation through its ability to inhibit cyclooxygenase-2 (COX-2) (13).

Alpha-lipoic acid is an endogenously produced antioxidant, though some data support that supplementation also improves insulin sensitivity (14). Evidence indicates that ginseng and magnesium may improve insulin secretion/sensitivity (15-16), while chromium and oat bran may improve glycemic control in patients with type 2 diabetes (17-18). Supplements with anti-cancer properties often modulate cell cycles and help eliminate abnormal cells that may become cancerous. Allyl sulfides, which constitute approximately 94% of the active compounds in garlic, are believed to suppress in vitro and in vivo growth of multiple types of cancer cells via apoptosis and cell cycle arrest (19). Unfortunately, evidence remains inconclusive for the benefit of many supplements in individuals with health issues or who are taking multiple over-the counter or prescription medications; a large number of studies in this field are limited by small sample sizes and/or poor study design.

Table 1. Permissible Dietary Supplement Label Claims and Guidance as Established by DSHEA

Three Categories of Claims Allowed for Dietary Supplements (24)	
Health Claims	Describe the connection between a nutrient or food substance and a disease or health related condition. FDA reviews scientific evidence or statements from authoritative scientific bodies before approving health claims.
Nutrient Content Claims	Describe the level of a nutrient in a food or dietary supplement.
Structure/Function Claims	Describe the role of a nutrient or dietary supplement intended to affect the structure or function of the body, the mechanism of how it maintains that structure or function, or general well being. FDA does not pre-approve structure/function claims so they must include the disclaimer "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Structure/function claims must be substantiated with "competent and reliable scientific evidence".

Legislation

Though plants have long been considered the "medicine of mankind," it was reasoned that scientific discoveries, growth and sophistication of the pharmaceutical industry and government oversight would give consumers what nature could not – safe and effective medicines that are consistent from dose to dose. But a series of events in the early to mid 20th century cast doubt on this assumption and prompted Congress to pass regulations (20-23) intended to establish a pharmaceutical industry based on "purity, truth in labeling, and effectiveness" (20). The Dietary Supplement and Health Education Act (DSHEA) was passed almost 20 years ago to define and provide a regulatory framework specifically for dietary supplements. To prevent manufacturers from making unsubstantiated claims regarding supplements, DSHEA established specific guidelines for dietary supplement labels. Table 1 summarizes those guidelines.

Health Risks of Herbal Supplements

Critics of DSHEA argue that herbal supplements suffer from the same safety concerns that existed when pharmaceutical medicines were first developed; that a lack of standardization and quality control poses risk to the integrity of the product and consumer safety. In fiscal year 2011, FDA records indicate that 1,777 mandatory adverse event reports were submitted from the dietary supplement industry (25), while US Poison Control Centers recorded 29,000 calls regarding use of dietary supplements in 2009, with 500 related to moderate to severe events (26). Potential safety risks posed by dietary supplements may be mitigated by evidence-based patient education provided by RDs.

Herbal Supplements, Medical Practice, and the role of the RD

Significant numbers of Americans do not share information regarding use of dietary supplements with their health care team; one study suggested that 70% of patients surveyed failed to disclose their use of herbal supplements during preoperative assessment (27). Failure to communicate with health professionals regarding use of dietary supplements may result in unidentified adverse interactions between prescribed medication, over-the-counter medication, foods, and supplements. As distinctions between fortified foods, functional foods, medical foods and dietary supplements continue to narrow, the need for patient education becomes more important. RDs routinely evaluate the use of dietary supplements within a comprehensive nutrition assessment, and should integrate education and counseling on supplements into their nutrition practices.

- The Academy of Nutrition and Dietetics describe RDs as the "consumers' bridge between evidence-based research and optimal health" (28). The Academy's Position Paper on Functional Foods states that RDs should incorporate functional food assessment into evidence-based nutrition practice.
- RD knowledge of DSHEA provides a strong background for answering legislative questions on herbal and other dietary supplements.
- RDs should provide patient education and report (MedWatch) any potential interactions between herbal supplements and prescription drugs.
- RDs already examine interrelationships between food, functional foods, and prescribed drugs on nutrition outcomes. Assessing effects of herbal supplements, either on promoting or managing nutritional health, is an appropriate extension of that role.

(Continued on page 22)

Table 2. Evidence of Efficacy of Select Herbal Supplements used by Cancer Survivors

Agent	Reported Benefits/Concerns	Evidence	RD Message
Black Cohosh (Cimmicifua Racemosa): Rhizome and roots are used in herbal treatments. Remifemin®, a commercial preparation of black cohosh, provides 10 mg root/rhizome per tablet.	**Reported Benefits:** Suppresses symptoms associated with menopause, such as hot flashes; cancer treatment **Potential Concerns:** May be toxic to the liver (29)	• Meta-analysis concluded that evidence is insufficient for recommending black cohosh as a treatment for menopausal symptoms (30). • In a six-month study, black cohosh was more effective than fluoxetine for treating hot flashes and night sweats associated with menopause (31). • German Commission E has found black cohosh to be effective at treating nervous system complaints such as tension associated with menopause (32). • No evidence suggests black cohosh may be effective as an anticancer treatment, but it may interfere with conventional cancer treatments including tamoxifen (33), and may increase toxic effects of doxorubicin and docetaxel (34).	• Some studies suggest that Black Cohosh may reduce menopausal symptoms, but the body of evidence does not support its use. • No evidence supports the use of black cohosh in cancer treatment. • Black cohosh may interfere with some conventional cancer treatments (33-34). • Black cohosh may be toxic to the liver (29).
Garlic: This perennial bulb is used in cooking and as an herbal treatment.	**Reported Cancer Benefit:** May stimulate apoptosis and help regulate cell cycles **Potential Concerns:** May interfere with function of some prescription drugs, including saquinavir and antiplatelet medications (35)	• Study suggested that 200 milligrams (mg) synthetic allitridum and 100 micrograms (mcg) selenium, given every other day, reduced risk for all tumors by 33% and risk of stomach cancer by 52% when compared with placebo (36). • Allyl sulfides, which comprise 94% of compounds in garlic, may promote apoptosis, cell cycle arrest, and inhibit growth of tumor cells (19).	• Garlic contains compounds that show potential as anti-cancer treatments. However, current evidence is insufficient for recommending garlic supplements for cancer treatment. • Garlic may interfere with the activity of some medications, in particular anticoagulant drugs (35).
Ginger (Zingiber officinale): The rhizome is used as an herbal treatment.	**Reported Cancer Benefit:** Manage nausea associated with chemotherapy **Potential Concerns:** may interfere with the activity of anticoagulant drugs, but evidence is equivocal (37)	• Study suggested that 0.5-1.0 g ginger/day significantly reduced severity of acute chemotherapy-induced nausea in adult cancer patients (38). • Study suggested that 1.0-2.0 g ginger taken daily for 3 days, given with antiemetic medicine, did not reduce the prevalence or severity of acute or delayed nausea (39).	• Evidence examining the effect of ginger on nausea and vomiting associated with chemotherapy is mixed. Current evidence is insufficient for confidently recommending ginger supplements for anti-emetic treatment.
Gingko Biloba: Seeds and leaves of gingko biloba are used in herbal treatments.	**Reported Cancer Benefit:** May inhibit proliferation of cancer cells **Potential Concerns**: Side effects are uncommon; there is concern that gingko may increase bleeding risk, but evidence is inconclusive (40)	• Gingko Evaluation of Memory (GEM) study found that those who received gingko (as opposed to a placebo) were not less likely to develop cancer over a 6-year period (41). • Treatment of pancreatic cell lines with 70uM kaempferol (an active component of gingko) for 4 days significantly inhibited cell proliferation (42).	• Cell studies suggest that researchers should explore the anticancer potential of gingko but at this time evidence is insufficient for recommending gingko for cancer treatment.
St. John's Wort (Hypericum perforatum): St. John's Wort is a bush that usually blooms around June 24th, the birthday of St. John the Baptist. Yellow flowers from this bush are used as herbal remedies.	**Reported Cancer Benefit:** May make cancer cells more sensitive to photodynamic (light) therapies **Potential Concerns:** May interact with many medications including warfarin (43)	• In the VITamins And Lifestyle cohort (VITAL study), use of St. John's Wort was inversely associated with risk of colorectal cancer (44). • Cell and animal studies suggest that St. John's wort may make cancer cells more sensitive to photodynamic (light) therapies, and therefore may have potential to improve anti-cancer effects of these modalities (45).	• Current evidence is insufficient for recommending St. John's wort for cancer treatment. • St John's wort induces CYP3A4, resulting in lower plasma levels of drugs that are CYP3A4 substrates, including cyclosporine, simvastatin, warfarin, and amitriptyline (43).
Curcumin (cucurma longa): Found in turmeric, the rhizome of curcumin is used in herbal treatments.	**Reported Cancer Benefit:** May inhibit growth of cancer cells; has anti-inflammatory and antioxidant properties **Potential Concerns:** May prolong activated partial thromboplastin time (aPTT) and prothrombin time (PTT) (46).	• Inhibited growth of esophageal cancer cells in vitro, (47). • The common dose used in clinical trails is 4 grams of curcumin daily for 30 days. • In a phase I trial for advanced and metastatic breast cancer, 8,000 mg/day was the maximal tolerated dose (48). • Piperine, a spice in black pepper, improves the absorption and bioavailability of curcumin in rats and humans without adverse effects (49). However, piperine may slow clearance of several drugs including phenytoin (Dilantin), propranolol (Inderal), and theophylline (50).	• The bioavailability of curcumin is low, thus increasing the pill burden. Piperine, a spice in black pepper, improves curcumin absorption but slows clearance of several drugs (49-50). • Emerging research suggests that curcumin should undergo further study for anticancer effects, but at this time evidence is insufficient for recommending curcumin for cancer treatment.

Table 3. Evidence of Efficacy of Select Herbal Supplements used by Patients with Diabetes

Agent	Reported Benefit / Concern	Evidence	RD Message
Fenugreek (*Trigonella foenugraecum*): Most research studies administer fenugreek seed powders.	Glycemic control	• Ten (10) grams (g)/day to 100 g/day resulted in significant reductions in fasting blood glucose (FBG) in Type 2 Diabetes Mellitus (T2DM) (51) and Type 1 Diabetes Mellitus (T1DM) patients (52). • May reduce FBG and A1C when taken with a sulfonylurea (53). • No impact on postprandial glucose values compared to placebo conditions (54).	• Study designs and dosages have been inconsistent. The effectiveness of fenugreek supplementation in glycemic control is unclear. • Fenugreek may interact with anticoagulants and MAOIs.
American Ginseng (*Panax quinquefolius*): Dried root of ginseng plants are used in ginseng supplements.	Glycemic control, insulin secretion	• In T2DM patients 3g dosage reduced FBG and A1C (55) and postprandial glucose (56). Higher dosages demonstrated no further benefit (56). • *In vitro* study indicated that American ginseng stimulates insulin production and reduces pancreatic beta cell apoptosis (15), though human study demonstrated no change in fasting insulin values with American ginseng supplementation (57).	• Research results are limited by small sample sizes (n=9-24), though preliminary evidence suggests that American ginseng may play a role in normalizing glucose metabolism. • Delayed onset of hypoglycemia may be a side effect of American ginseng, so blood glucose should be monitored closely. • American ginseng may interact with warfarin, MAOIs, estrogens, nifedipine, and loop diuretics.
Cinnamon (*Cinnamomum aromaticum*): A common spice used in culturally diverse cuisines, cinnamon is typically found as an encapsulated powder in herbal supplements.	Glycemic control	• In T2DM patients 1-6 g/daily intake of cinnamon capsules significantly reduced FBG (58), while 1 g/daily reduced A1C by 0.83% (59). • Other research has shown no effect of cinnamon supplementation on A1C, FBG, or insulin sensitivity in T2DM patients (60-61). • A Cochrane systematic review and meta-analysis, which included a total of 577 participants, found no overall benefit of cinnamon supplementation on diabetes endpoints (61).	• Collectively, it appears that cinnamon likely has no substantial effect on glycemic control. • Cinnamon is high in coumarin and may cause hepatotoxicity in patients with liver disease.
Prickly Pear Cactus (*Opuntia streptocantha* or *Opuntia ficus indica*): A common foodstuff in Arizona and Mexico. Prickly pear is typically consumed as a dehydrated extract or by broiling the stems of the young plant.	Glycemic control	• Preliminary trials indicate that the stems, but no other part of the plant, may have hypoglycemic effects (62-64).	• All results are limited by study sample size (n=8-32). The only studies examining effects of prickly pear on glycemic control in humans were performed more than two decades ago. • Prickly pear is likely safe when consumed orally as a food.
Oat Bran: Oat bran is high in fiber, and commonly used for treating hypercholesterolemia. It is often consumed as oat bran flour.	Glycemic control (postprandial and 24-hour)	• Studies in T2DM patients indicate that long term and acute oat bran flour consumption reduces postprandial glucose (18,65-66).	• Oat bran is not approved by the German Commission E for diabetes treatment, though it has Generally Recognized as Safe (GRAS) status in the United States.
Chromium: Chromium is essential in carbohydrate and lipid metabolism. Brewer's Yeast is commonly used as a chromium supplement.	Glycemic control	• Daily supplementation with 40 to 1000 micrograms (µg) results in reductions in A1C, FBG, and postprandial glucose in T2DM patients (20, 67-68). • T2DM patients with well-controlled diabetes due to oral hypoglycemic agents do not benefit from 400 µg/day chromium supplementation in the form of chromium yeast (69).	• Studies examining effects of chromium on glucose control have been somewhat limited by sample size (n=3-180), so it is difficult to draw conclusions about efficacy. • Chromium supplements have not provided added benefit when glucose control is well established with oral hypoglycemic agents. • Chromium supplements (up to 1000 µg/day) have been found to be safe when used short term (up to 6 months of supplementation).
Magnesium (Mg^{2+}): Magnesium is an essential cofactor in enzymes/proteins involved in glucose metabolism, including the insulin receptor. It is sold in pill form but also can be administered as $MgCl_2$ liquid solution.	Insulin sensitivity, glycemic control	• A meta-analysis including over 536,000 prospective cohort study participants suggests an inverse relationship between risk of T2DM development and Mg^{2+} intake (dietary Mg intake and total Mg intake, which included intake from dietary supplements) (70). A dose-response analysis demonstrated a 14% reduction in risk of developing T2DM with 100 milligram (mg)/day incremental increases in Mg2+ intake (70). • Some studies suggest that Mg^{2+} supplementation can reduce FBG and improve insulin sensitivity (16,71), whereas others show no effect (72-73).	• Higher Mg^{2+} intake may reduce risk of developing T2DM, though study sample size limits the ability to draw conclusions regarding glycemic control once diabetes has developed. • Mg^{2+} supplementation is likely safe at doses up to the tolerable upper limit of 350 mg/day. However, it can cause diarrhea. You should mention this. It's a very common side effect with supplementation.
Selenium: Selenium is an essential cofactor in glutathione peroxidases. It is typically consumed as selenized yeast but also available in multivitamin-mineral preparations, and single mineral pills.	Increased risk of developing T2DM	• Epidemiological evidence suggests that higher serum selenium values are associated with an increased risk of T2DM (74). • Results from a large clinical trial suggest indicate an increased risk of developing T2DM in those randomized to consume 200 µg selenium/day for 7.7 years compared with placebo (75).	• Unless advised by an MD or an RD, supplements providing more than the DRI of 55 µg of selenium should be avoided.
Alpha-Lipoic Acid (ALA): A cofactor of many insulin sensitizing and glucose metabolism enzymes, ALA is usually taken as a capsule.	Improved insulin sensitivity, peripheral neuropathy	• Supplementation with 300 to 1800 mg daily for four weeks improves insulin sensitivity in T2DM patients (14, 76-77). • Improvements in symptoms of peripheral neuropathy including burning, pain, and numbness of the feet and legs was observed after 3 weeks of 600 mg/daily ALA supplementation (78-79). • Supplementation with 600 mg/daily was safe and reduced progression of neuropathy in diabetic patients (80).	• Evidence suggests that ALA may improve insulin sensitivity and reduce progression of peripheral neuropathy, over the short and long term. • Patients with T2DM should consult with a qualified medical professional regarding use of this product. • ALA is expensive, and Vitamin E produces similar results,but at a reduced cost.
Coenzyme Q10 (CoQ):	Improved A1C levels	• Some studies show reductions in A1C in individuals with T2DM who consume 200 mg CoQ for 12 weeks (81-82). • Study providing 200 mg CoQ for 12 weeks found no effect on A1C or any other diabetes-associated outcomes (83).	• Few studies have tested the role of CoQ in altering diabetes outcomes, though it is used in patients with neurological disorders, heart failure, hypertension, and in those taking statins. • There is insufficient data to make a recommendation for the supplementation of CoQ in diabetics seeking A1C reduction.

Conclusion:

Individuals with cancer and/or diabetes commonly consume dietary supplements. Some of these products have demonstrated efficacy as a part of nutritional therapy, others do not, and still others may be associated with adverse health consequences. Their unique knowledge and skill set positions the RD as a provider of assessment and education on evidence-based information on benefits, risks and potential interactions between dietary supplements, food, and prescription and non-prescription medicines. Tables 2 and 3 summarize current evidence of select supplements commonly used for the prevention and/or treatment of cancer and diabetes.

Caitlin Dow, PhD recently received her doctorate in Nutritional Sciences from the University of Arizona. Dr. Dow will be continuing her research career as a Research Associate in Vascular Biology in the Department of Integrative Physiology at the University of Colorado, Boulder.

Retired Captain Maureen Leser, MS, RD, CSO, LD, U.S. Public Health Service, is editor of Oncology Nutrition Connection, the newsletter of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics.

References

1. Alves R, Rosa IML. Biodiversity, traditional medicine and public health: where do they meet? *J Ethnobiol Ethnomedicine*. 2007;3:14
2. Wachtel-Galor S, Benzie IF. Herbal Medicine. An introduction to its history, usage, regulation, current trends, and research needs. In: Benzie IFF, Wachtel-Galor S, eds. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd ed. Boca Raton, FL: CRC Press; 2011:chapter 1.
3. Rock CL. Multivitamin-multimineral supplements: who uses them? *Am J Clin Nutr.* 2007; 85(1):277S-279S.
4. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003-2006. *J Nutr.* 2011;141(2):261-266.
5. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report* 2008;10:1–23.
6. van Tonder E, Herselman MG, Visser J. The prevalence of dietary-related complementary and alternative therapies and their perceived usefulness among cancer patients. *J Human Nutr Diet.* 2009;22(6);528-535.
7. Bardia A, Greeno E, Bauer BA. Dietary supplement usage by patients with cancer undergoing chemotherapy: does prognosis or cancer symptoms predict usage? *J Support Oncol.* 2007;5(4):195-198.
8. Miller MF, Bellizzi KM, Sufian M, Ambs AH, Goldstein MS, Ballard-Barbash R. Dietary supplement use in individuals living with cancer and other chronic conditions: a population-based study. *J Am Diet Assoc.* 2008;108(3):483-494.
9. Richardson MA. Biopharmacologic and herbal therapies for cancer: research update from NCCAM. *J Nutr.* 2001;131(11 Suppl):3037S-3040S.
10. Ferrucci LM, McCorkle R, Smith T, Stein KD, Cartmel B. Factors related to the use of dietary supplements by cancer survivors. *J Altern Complement Med.* 2009;15(6):673-680.
11. Nahin RL, Byrd-Clark D, Stussman BJ, Kalyanaraman N. Disease severity is associated with the use of complementary medicine to treat or manage type-2 diabetes: data from the 2002 and 2007 National Health Interview Study. *BMC Complement Altern Med.* 2012;12:193.
12. Odegard PS, Janci MM, Foeppel MP, Beach JR, Trence DL. Prevalence and correlates of dietary supplement use in individuals with diabetes mellitus at an academic diabetes care clinic. *Diabetes Educ.* 2011;37(3):419-425.
13. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. *Adv Exp Med Biol*. 2007;595:105-125.
14. Ansar H, Mazloom Z, Kazemi F, Hejazi N. Effect of alpha-lipoic acid on blood glucose, insulin resistance and glutathione peroxidase of type 2 diabetic patients. *Saudi Medical Journal*, 2011;32(6):584-588.
15. Luo JZ, Luo L. American ginseng stimulates insulin production and prevents apoptosis through regulation of uncoupling protein-2 in cultured beta cells. Evidence-based complementary and alternative medicine: eCAM, 2006;3(3):365-372.
16. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care.* 2003;26(4):1147-1152.
17. Sharma S, Agrawal RP, Choudhary N, Jain S, Goyal S, Agarwal V. Beneficial effect of chromium supplementation on glucose, HbA1C and lipid variables in individuals with newly onset type-2 diabetes. *J Trace Elem Med Biol.* 2011;25(3):149-153.
18. Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. *Nutr Met Cardiovasc Dis.* 2005;15(4): 255-261.
19. Wang H-C, Pao J, Lin S-Y, Sheen L-Y. Molecular mechanisms of garlic-derived allyl sulfides in the inhibition of skin cancer progression. *Ann NY Acad Sci.* 2012;1271(1):44-52.
20. Talalay P, Talalay P. The importance of using scientific principles in the development of medicinal agents from plants. *Acad Med.* 2001;76:238-247.
21. Barkan ID. Industry invites regulation: the passage of the Pure Food and Drug Act of 1906. *Am J Public Health.* 1985;75:18-26.
22. The new federal laws relating to foods, drugs, and cosmetics. *Am J Public Health and the Nation's Health.* 1938;28(9):1114-1116.
23. Greene JA, Podolsky SH. Reform, regulation, and pharmaceuticals – The Kefauver-Harris amendments at 50. *N Engl J Med.* 2012;36:1481-1483.
24. S.784 Dietary Supplement Health and Education Act of 1994. Public Law 103–417, 1994.
25. Federal Register volume 77, number 57 (Friday, March 23, 2012). From the Federal Register Online via the Government Printing Office (www.gpo.gov).
26. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clinical Toxicology* 2010; 48:979–1178.
27. Kaye AD, Clarke C, Sabar R, Vig S, Dhawan KP, Hofbauer R. Herbal medications: current trends in anesthesiology practice-a hospital survey. *J Clin Anesth.* 2000;12:468-471.
28. Hasler CM, Brown AC, Burns JA. Position of the American Dietetic Association: Functional Foods. *J Am Diet Assoc.* 2009;109:735-746.
29. Madahy GB, Low-Dog TL, Barrett ML, Chavez ML, Gardiner P, Ko R. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause*. 2008;15(4 Pt 1):628-638.
30. Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. *Cochrane Database Syst Rev.* 2012 Sep 12;9:CD007244.
31. Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeynelogluy HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *Adv Ther.* 2007;24(2):448-461.
32. Bundesanzeiger (Cologne, Germany): January 5, 1989
33. Li J, Gödecke T, Chen SN, et al. In vitro metabolic interactions between black cohosh (Cimifuga racemosa) and tamoxifen via inhibition of cytochromes P450 2D6 and 3A4. *Xenobiotica*. 2011;41(12):1021-1030.

34. Rockwell S, Liu Y, Higgins SA. Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine black cohosh. *Breast Cancer Res Treat* 2005;90(3):233-239.
35. National Center for Complementary and Alternative Medicine (NCCAM). Herbs at a glance: Garlic. http://nccam.nih.gov/health/garlic/ataglance.htm Updated April 12, 2012, Accessed 5/3/13.
36. Li H, Li HQ, Wang Y, et al. An intervention study to prevent gastric cancer by micro-selenium and large dose of allitridum. *Chinese Medical Journal* (English). 2004;117(8):1155-1160.
37. Janssen PL, Meyboom S, van Staveren WA et al. Consumption of ginger (Zingiber officinale Roscoe) does not affect ex vivo platelet thromboxane production in humans. *Eur J Clin Nutr.* 1996;50:772-774.
38. Ryan JL, Heckler CE, Roscoe JA, Dakhil SR, Kirshner J, Flynn PJ. Ginger (zingiber officinale) reduces acute chemotherapy-induced nausea: A URCC CCOP study of 576 patients. *Support Care Cancer.* 2012;20(7):1479-1489.
39. Zick SM, Ruffin MT, Lee J, et al. Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. *Support Care Cancer.* 2009;17(5):563-572.
40. Roland PD, Nergard CS. Ginkgo biloba-effect, adverse events and drug interactions. *Tidsskr Nor Laegeforen*. 2012.143(8):956-959.
41. Biggs ML, Sorkin BC, Nahin RL, Kuller LH, Fitzpatrick AL. Ginkgo biloba and risk of cancer: secondary analysis of the ginkgo evaluation of memory (GEM) study. *Pharmacoepidemiol Drug Saf.* 2010;19(7):694-698.
42. Zhang Y, Chen AY, Chen C, Yao Q. Ginkgo biloba extract kaempferol inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. *J Surg Res.* 2008;148(1):17-23.
43. Roby CA, Anderson GD, Kantor E, Dryer DA, Burstein AH. St. John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther.* 2000;67(5):451-457.
44. Satia JA, Littman A, Slatore CG, Galanko JA, White E. Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins And Lifestyle(VITAL) study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(5):1419-1428.
45. Wessels JT, Busse AC, Rave-Fränk M, et al. Photosensitizing and radiosensitizing effects of hypericin on human renal carcinoma cells in vitro. *Photochem Photobiol.* 2008;84(1):228-35.
46. Kim DC, Ku SK, Bae JS. Anticoagulant activities of curcumin and its derivative. *BMB Reports Online (Korean Society for Biochemistry and Molecular Biology)*. 2012;45(4):221-226.
47. Subramaniam D, Ponnurangam S, Ramamoorthy P, et al. Curcumin induces cell death in esophageal cancer cells through modulating notch signaling. PLoS One. 2012; 7(2): e30590. Published online 2012 February 17.
48. Bayet-Robert M, Kwiatkowski F, Leheurteru M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biology & Therapy.* 2010;9(1):8-14.
49. Bano G, Raina RK, Zutshi U, Bedi KL, Johri RK, Sharma SC. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. *Eur J Clin Pharmacol.* 1991;41(6):615-617.
50. Velpandian T, Jasuja R, Bhardwaj RK, Jaiswal J, Gupta SK. Piperine in food: interference in the pharmacokinetics of phenytoin. *Eur J Drug Metab Pharmacokinet.* 2001;26(4):241-247.
51. Kassaian N, Azadbakht L, Forghani B, Amini M. Effect of fenugreek seeds on blood glucose and lipid profiles in type 2 diabetic patients. *Intl J Vit Nutr Res.* 2009;79(1):34-39.
52. Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type 1 diabetes. *Eur J Clin Nutr.* 1990;44(4):301-306.
53. Lu FR, Shen L, Qin Y, Gao L, Li H, Dai Y. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sulfonylureas in the treatment of type 2 diabetes mellitus. *Chinese J Integrative Med.* 2008;14(1):56-60.
54. Losso JN, Holliday DL, Finley JW, et al. Fenugreek bread: a treatment for diabetes mellitus. *J Medicinal Food.* 2009;12(5):1046-1049.
55. Vuksan V, Sievenpiper JL, Xu Z, et al. Konjac-Mannan and American ginseng: emerging alternative therapies for type 2 diabetes mellitus. *J Am Coll Nutr.* 2001;20(5Suppl): 370S-380S; discussion 381S-383S.
56. Vuksan V, Stavro MP, Sievenpiper JL, Beljan-Zdravkovic U, Leiter LA, Josse RG. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes Care.* 2000;23(9):1221-1226.
57. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care.* 2003;26(12):3215-3218.
58. Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. *J Am Board Fam Med.* 2009;22(5):507-512.
59. Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. Effect of cinnamon on glucose control and lipid parameters. *Diabetes Care.* 2008;31(1):41-43.
60. Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. *J Nutr.* 2006;136(4):977-980.
61. Leach MJ, Kumar S. Cinnamon for diabetes mellitus. Cochrane database of systematic reviews. 2012. 9:p.CD007170.
62. Frati-Munari AC, Gordillo BE, Altamirano P, Ariza CR. Hypoglycemic effect of Opuntia streptacantha Lemaire in NIDDM. *Diabetes Care.* 1988;11(1):63-66.
63. Frati-Munari AC, et al. Hypoglycemic action of different doses of nopal (Opuntia streptacantha Lemaire) in patients with type II diabetes mellitus. *Arch Invest Med (Mex)*. 1989;20(2):197-201.
64. Frati Munari AC, Lastra VO, Andraca CRA. Evaluation of nopal capsules in diabetes mellitus. *Gaceta Medica de Mexico.* 1992;128(4):431-436.
65. Pick ME, Hawrysh ZJ, Gee MI, Toth E, Garg ML, Hardin RT. Oat bran concentrate bread products improve long-term control of diabetes: a pilot study. *J Am Diet Assoc.* 1996;96(12):1254-1261.
66. Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *New Eng J Med.* 2000;342(19):1392-1398.
67. Anderson RA, Cheng N, Bryden NA, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes*. 1997;46(11):1786-1791.
68. Racek J, Trefil L, Rajdo D, Mudrova V, Hunter D, Senft V. Influence of chromium-enriched yeast on blood glucose and insulin variables, blood lipids, and markers of oxidative stress in subjects with type 2 diabetes mellitus. *Biol Trace Elem Res.* 2006;109(3):215-230.
69. Kleefstra N, Houweling ST, Bakker SJ, et al. Chromium treatment has no effect in patients with type 2 diabetes in a Western population: a randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2007;30(5):1092-1096.
70. Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type2 diabetes: meta-analysis of prospective cohort studies. *Diabetes Care.* 2011;34(9):2116-2122.
71. Yokota K, Kato M, Lister F, Ii H, Hayakawa R, Kikuta T. Clinical efficacy of magnesium supplementation in patients with type 2 diabetes. *J Am Coll Nutr.* 2004;23(5):506S-509S.
72. De Valk HW, Verkaaik R, van Rijn HJ, Geerdink RA, Struyvenberg A. Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med.* 1998;15(6):503-507.

(Continued on next page)

73. Gullestad L, Jacobsen T, Dolva LO. Effect of magnesium treatment on glycemic control and metabolic parameters in NIDDM patients. *Diabetes Care.* 1994;17(5):460-461.
74. Bleys J, Navas-Acien A, Guallar E. Serum selenium and diabetes in U.S. adults. *Diabetes Care.* 2007;30(4):829-834.
75. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med. 2007*;147(4):217-223.
76. Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. *Free Rad Biol Med.* 1999;27(3-34):309-314.
77. Konrad T, Vicini P, Kusterer K, Hoflich A, Assadkhani A, Bohles HJ. Alpha-Lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. *Diabetes Care.* 1999;22(2):280-287.
78. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care.* 1999;22(8):1296-1301.
79. Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diab Med.* 1999;16(12):1040-1043.
80. Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R. Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. *Diabetes Care.* 2011;34(9):2054-2060.
81. Hodgson JM, Watt GF, Playford DA, Burke V, Croft KD. Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr.* 2002;5(11):1137-1142.
82. Playford DA, Watts GF, Croft KD, Burke V. Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type2 diabetes. *Atherosclerosis*. 2003;168(1):169-179.
83. Eriksson JG, Forsen TJ, Mortensen SA, Rohde M. The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. *Biofactors*. 1999;9(2-4):315-318.

Can Persons with Diabetes Consume Sugar and Control Blood Glucose Levels?

Megan Robinson, MS, RD, CDE, LDN

Abstract

Even as the "diabetic diet" has evolved throughout the years, one well-established fact is that carbohydrates have the greatest effect on postprandial blood glucose levels (1). The total amount of carbohydrate consumed has been the primary focus for achieving healthy blood glucose control while maintaining a flexible and varied diet. However, research has shown that in addition to the total amount, the type of carbohydrate also may affect the glycemic response. In particular, researchers and clinicians continue to discuss whether individuals with diabetes may include foods containing added sugars within their meal plans without compromising glycemic control.

Introduction

The primary goal of diabetes care is to safely maintain blood glucose levels within the normal range (2). Diet alone or diet coupled with insulin and/or non-insulin diabetes medication has been the cornerstone to achieving this control. However, the concept that a person who has diabetes cannot eat foods containing added sugar continues to be discussed by diabetes researchers and educators (2). According to the American Diabetes Association (ADA), not only does the total amount of carbohydrate affect postprandial blood glucose response, but the type of carbohydrate may also affect the response (2). Studies have documented that the type of carbohydrate may affect diabetes control, but the total carbohydrate ingested may be related to a greater glucose response than a particular type. The objectives of this article are to review the history of the diabetic diet, explain carbohydrate metabolism in relation to blood glucose response, and provide carbohydrate and sugar intake recommendations for diabetes based on recommendations of the ADA and the Academy of Nutrition and Dietetics (AND).

History of Diabetic Diets

Before the discovery of insulin in 1921, a person with diabetes was instructed to eat a low-calorie, low-carbohydrate diet that included less than 100 g/day of carbohydrate to prevent ketoacidosis (3). Over the years, the "diabetic diet" has evolved from an exchange system, in which one type of carbohydrate food is exchanged for another of equal carbohydrate value, to a more flexible approach of carbohydrate counting. Overly restrictive carbohydrate diets in the 1960s and 1970s proved difficult to follow, resulting in poor compliance and inadequate blood glucose control (4). In the late 1980s, the ADA revised the exchange system and made additional nutrition recommendations regarding fat, fiber, glycemic index, and non-nutritive sweeteners (5). In addition, the ADA abandoned the term "diabetic diet" and promoted individualized meal planning.

Since the Diabetes Control and Complications Trial in the 1990s, carbohydrate counting has become an effective and realistic approach for managing diabetes. One popular nutrition approach is the Dose Adjustment for Normal Eating (DAFNE) (6-7). This approach has allowed people with type 1 diabetes (T1DM) and/or type 2 diabetes (T2DM) requiring insulin to match the grams of carbohydrate consumed to the amount of fast-acting insulin needed to

maintain blood glucose within a healthy range. A recent DAFNE study involving persons with T1DM determined that this approach resulted in improved blood glucose control (improved glycolated hemoglobin (A1C)) by at least 0.5% in those whose baseline mean A1C value was 9.6% or greater); a 40% reduction in the incidence of hypoglycemia; no occurrence of diabetic ketoacidosis; and most importantly, the freedom and flexibility to consume a wider variety of foods (7). This approach also was associated with a decreased incidence of depression as well as relief of distress related to diabetes care (6-7). In persons with T2DM who do not require insulin, carbohydrate counting or portion control with carbohydrates is an effective approach to managing weight and blood glucose control (2,8).

Regardless of the changes to the "diabetic diet" throughout the years, carbohydrates remain the factor that has the greatest impact on postprandial glucose response. However, those diagnosed with diabetes and their clinicians still want to know whether eating foods with added sugars affects the glucose response more than the total amount of carbohydrate consumed.

Carbohydrate: Amount Versus Type

Carbohydrate Amount

Counting carbohydrates and matching fast-acting insulin (lispro, glulisine, or aspart) to the total grams of carbohydrates eaten provides a flexible approach to managing diabetes. This technique assumes that only the total amount of carbohydrate consumed, not the type, affects blood glucose values. According to the ADA, a diet that includes carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat milk is recommended for good health and diabetes control (2). Expert panels have recommended that total carbohydrates comprise 45% to 65% of total calories (2,9). Following a nutrition assessment, the registered dietitian (RD) recommends the most appropriate carbohydrate intake for each person with diabetes, incorporating the patient's weight, height, age, activity level, previous diet and medical history into the recommendation. The most recent ADA Position Statement (2012) recommends eating at least 130 g carbohydrate daily from a variety of carbohydrate sources to provide adequate glucose to fuel the central nervous system (9); this recommendation is consistent with the Dietary Reference Intake for carbohydrate, as recommended by the Institute of Medicine (10).

Table 1. Statements Regarding Sucrose Use

Expert Committee	Percentage of Sucrose of Total Energy Needs
Academy of Nutrition and Dietetics (13)	Sucrose containing foods should be substituted for other carbohydrates; intakes of 10 % to 35% do not have a negative effect on glycemic response when substituted
International Society for Pediatric and Adolescent Diabetes (9)	Moderate sucrose intake; up to 10% of total energy
Institute of Medicine (10)	Intakes of added sugars to not exceed 25% of energy to ensure adequate intake of essential nutrients

Table 2. Glycemic Index Values for Various Types of Sugars (18)

Type of Sugar	Glycemic Index Value
Glucose	100
Sucrose (glucose and fructose)	61
Fructose	23
Honey (fructose and glucose)	58 to 87
Lactose (glucose and galactose)	46

Type of Carbohydrate

The effect of the type of carbohydrate on blood glucose control continues to be debated. A common belief is that individuals with diabetes should not eat foods containing added sugar because they cause a rapid rise in blood glucose concentrations. This belief originated from a study in the 1920s, which demonstrated a greater blood glucose rise in pancreatectomized dogs after eating glucose when compared with starch (11). In 1978, Wahlqvist and colleagues demonstrated that monosaccharides and disaccharides greatly affect the blood glucose response, but no more than polysaccharides (i.e., starch) (12). The Academy's Evidence Analysis Library (EAL) suggests that a person with diabetes can consume foods containing sucrose without compromising glucose control as long as these foods are counted as part of the total carbohydrate consumed and not as additional carbohydrate intake (13). The EAL (13) states "Sucrose intakes of 10 to 35 percent of total energy intake do not have a negative effect on glycemic or lipid responses when substituted for isocaloric amounts of starch." This expert committee suggests that consuming calories from sucrose does not negatively affect blood glucose or lipid concentrations (13). According to the International Society for Pediatric and Adolescent Diabetes, sucrose does not increase blood glucose levels more than starches containing similar caloric amounts (9). Even though recommendations pertaining to the percentages of total calories from sucrose vary (Table 1), the important message is to avoid excess energy intake from sucrose, which will allow for a more nutrient-dense diet and help prevent excessive weight gain.

Glycemic Index

Taking a flexible approach to carbohydrate counting and incorporating limited amounts of added sugars into energy needs

(Continued on next page)

is a practical approach to managing diabetes. Studies have determined that the glycemic index (GI) may provide additional benefit in controlling blood glucose (11). Although use of the GI continues to be debated, it is a simple approach that in addition to carbohydrate counting may improve glycemic control.

The GI is a classification of foods based on their impact on glycemic effect over a 2-hour period. It compares 50 g of carbohydrate of a test food to 50 g of glucose or white bread (15). The GI system ranks food, on a scale of 0 to 100, according to each food's ability to raise blood glucose concentrations. Low-GI food levels range from 0 to 55, medium-GI foods range from 56 to 69, and high-GI foods range from 70 to 100. Foods with a low GI raise blood glucose concentrations less rapidly than do foods with a high GI (16-18).

According to the GI scale, a variety of sugars affect the postprandial glycemic response differently (Table 2) (15-18). Glucose is a high-GI sweetener (GI 100), whereas fructose is categorized as a low-GI sweetener (GI 23). Even though fructose does not produce a rapid postprandial glucose response when compared to sucrose or glucose, sugar products containing fructose, such as high fructose corn syrup, are associated with a variety of adverse health effects including a negative effect on lipid levels (19-20). Fructose should be predominantly consumed in its natural state, found in whole fruits and vegetables (2).

A study conducted in 2011 determined that the GI value accounted for 10% to 18% of the glycemic variability in overweight and obese adults with T2DM, independent of the total calorie and carbohydrate intake (15). Research on the effects of GI studied in the pediatric population with T1DM (ages 7 through 16 years) has yielded similar results, indicating that consuming a low-GI diet may improve glucose control (16). Subjects in the low-GI group had lower daytime mean blood glucose values, despite a larger amount of carbohydrates consumed per unit of insulin, compared to those in the high-GI group.

The specific GI value produced by individual foods or sugars does not determine the glycemic response alone. Critics of the GI argue that this unrealistic approach limits eating a variety of healthy foods, especially in the pediatric population, leading to noncompliance and poor adherence to diet recommendations (17). Another concern is that low-GI foods may be higher in total fat compared to high-GI foods. For example, a Snickers® candy bar is listed as having a medium GI of 55 and watermelon is categorized as having a high GI of 72 (18). The candy bar obviously is less nutrient-rich than fruit, and most RDs would recommend eating whole fruit despite the higher GI. Furthermore, variables such as type of starch, cooking method and time, ripeness, acidity, and degree of processing all affect the GI and postprandial glucose response (2). Finally, the GI focuses on individual foods rather than on realistic mixed meals and only considers the type of carbohydrate rather than the total amount consumed.

Clinical Application

RDs should emphasize that the total amount of carbohydrate consumed greatly affects the postprandial glycemic response. Using the DAFNE approach, RDs can educate individuals with diabetes on how to match fast-acting insulin to the grams of carbohydrate they eat to increase variety in their diets.

When providing education on carbohydrate counting, RDs should stress the importance of eating nutrient-rich carbohydrate foods, including whole grains, fruit, vegetables, legumes, and low-fat milk, but they also should explain how to incorporate added sugars into the diet. It is unrealistic to expect that individuals with diabetes will consume no added sugars. The recommended amount of added sugars varies, but added sugars should be counted as part of the total amount of carbohydrates consumed, in order to prevent excessive weight gain and to promote a healthy diet.

RDs can discuss the benefits of using the GI in addition to carbohydrate counting but should also review the limitations of solely using the GI and encourage consumption of nutrient-rich foods, such as fruit, despite the GI value. Overall, carbohydrate counting combined with choosing healthier types of carbohydrates (e.g., whole grains) should be the focus of nutrition education for individuals with diabetes. However, to improve compliance and flexibility with the diet, added sugars can be incorporated within the total amount of carbohydrates recommended without negatively affecting glycemic control.

Conclusion

Today, individuals with diabetes can eat varied diets, including a limited amount of added sugars, as recommended by the Dietary Guidelines for Americans for the general population (10). The term "diabetic diet" is no longer used to describe an inflexible meal plan lacking in variety and added sugars. Added sugars can be incorporated into the diet in moderation without resulting in hyperglycemia, as long as fast-acting insulin is matched to the total amount of carbohydrate consumed and the added sugar is counted within the total carbohydrate count of the meal. Overly restrictive diets and denying all added sugars is an unrealistic approach to diabetes management. However, if sugar is added to a meal or snack, the amount of other carbohydrate should be reduced to prevent excessive energy intake. Even though the amount of carbohydrate has a significant impact on glucose response, the type of carbohydrate may also affect postprandial glucose values, depending on the GI. Research has shown that the combination of the amount of carbohydrate and the GI value of carbohydrate account for approximately 90% of the blood glucose variability, suggesting that the amount and type of carbohydrate consumed can affect the glucose response and should be considered when evaluating the glycemic effect of food (1).

Megan Robinson, MS, RD, CDE, LDN ,is a clinical dietitian at The Children's Hospital of Philadelphia. Ms Robinson is affiliated with the Diabetes Center for Children and is a Certified Diabetes Educator.

References

1. Sheard N, Clark N, Brand-Mill J. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. *Diabetes Care.* 2004;27(9):2266-2271.
2. American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care.* 2008;1:S61-S78.
3. Wheeler M, Pi-Sunyer FX. Carbohydrate issues: type and amount. *J Am Diet Assoc.* 2008;108(4Suppl1):S34-S39.
4. Kawamura T. The importance of carbohydrate-counting in the treatment of children with diabetes. *Pediatr Diabetes.* 2007;8(6):57-62.
5. Powers M. A review of recent events in the history of diabetes nutritional care. *Diabetes Educ.* 1992;18(5):393-400.
6. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment for Normal Eating (DAFNE) randomized controlled trial. *BMJ.* 2002;325:1-6.
7. Keen AJ, Duncan E, McKillop-Smith A. Dose Adjustment for Normal Eating (DAFNE) in routine clinical practice: who benefits? *Diabetic Med.* 2011;29:670-676.
8. American Diabetes Association. Standards of medical care in diabetes-2012. *Diabetes Care.* 2012;35(supplement1):S11-S63.
9. Smart C, Aslander-van Vliet E, Waldron S. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium: nutritional management in children and adolescents with diabetes. *Pediatr Diabetes.* 2007;8:323-329.
10. Food and Nutrition Board. Dietary carbohydrates: sugars and starches. In: Dietary Reference Intakes. Washington, DC: National Academies Press; 2005. http://www.nap.edu/openbook.php?record_id=10490&page=265. Accessed February 2013.
11. Wolever T, Miller J. Sugars and blood glucose control. Am J Clin Nutr. 1995;62:212S-227S.
12. Wahlqvist ML, Silmshurst EG, Richardson EN. The effect of chain length on glucose absorption and the related metabolic response. *Am J Clin Nutr.* 1978;31(11):1998-2001.
13. American Dietetic Association. Evidence Analysis Library, http://www.adaevidencelibrary.com; American Diabetes Association. Nutrition recommendations and interventions for diabetes and Standards of medical care in diabetes. 2007.
14. Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. *J Acad Nutr Dietetics.* 2012;112:739-758.
15. Fabricatore A, Ebbeling C, Wadden T, Ludwig D. Continuous glucose monitoring to assess the ecologic validity of dietary glycemic index and glycemic load. *Am J Clin Nutr.* 2011;94:1519-1524.
16. Nansel T, Gellar L, McGill A. Effect of varying glycemic index meals on blood glucose control assessed with continuous glucose monitoring in youth with type 1 diabetes on basal-bolus insulin regimens. *Diabetes Care.* 2008;31:695-697.
17. Rovner A, Tonja N, Gellar L. The effect of a low-glycemia diet vs a standard diet on blood glucose levels and macronutrient intake in children with type 1 diabetes. *J Am Diet Assoc.* 2009;109:303-307.
18. Glycemic index. Diabetesnet.com. http://www.diabetesnet.com/food-diabetes/glycemic-index. Accessed October 2012.
19. Bantle J, Laine D, Thomas W. Metabolic effects of dietary fructose and sucrose in type I and II diabetic subjects. *JAMA.* 1986;256:3241-3246.
20. Couch S, Crandell J, Shah A, et al. Fructose intake and cardiovascular risk factors in youth with type 1 diabetes: SEARCH for diabetes in youth study. Diabetes Research and Clinical Practice. 2013, http://dx.doi.org/10.1016/j.diabres.2013.03.013.

CPE Article Answer Key:

1. C	6. C
2. C	7. C
3. D	8. D
4. B	9. A
5. B	10. B

Acknowledgements

The editorial staff would like to thank the following people for assisting with the development of this issue. They include:

Sara Bergerson, MS, RD
Mridul Datta, PhD, RD
Rachael Drabot-Lopez, MPH, RD, CSO
Andrea Dunn, RD, LD, CDE
Linda Flanagan Vahl
Marion Franz, MS, RD, CDE
Jenny Gau, PharmD
Patsy Koonce, MS, RD, LDN
Paula Leibovitz, MS, RD, CDE, CD-N
Kathryn Mount, MS, RD, LDN
Gregg Simonson, PhD
Crystal Tallman, RD, LD, CSO
Erica Wheeler, PharmD

Case Study: Pancreatic Cancer and Secondary (Surgically Induced) Diabetes

Deborah Downes, RD, CSO, CD-N

Abstract

Pancreatic cancer and diabetes independently are serious diagnoses; when occurring as comorbid conditions, they can be complicated to manage. Insulin resistance and alterations in glucose metabolism may be early diagnostic indicators of pancreatic cancer. While overall prognosis of pancreatic cancer remains suboptimal, chemotherapy, radiation, and/or surgery are potential treatment options. Side effects of treatment commonly affect blood glucose values and must be addressed. Secondary diabetes can result from pancreatic resection or pancreatoduodenectomy (Whipple procedure) for pancreatic cancer. As the pancreatic cancer progresses, symptoms, medical nutrition therapy, and the goals of care will likely change. Registered Dietitians (RDs) should be involved in all stages of care, ideally from the initial diagnosis. A case is presented of a woman with pancreatic cancer who suffered from diabetic and nutritional complications. Unfortunately, an RD was not consulted until seven years after her initial diagnosis. Earlier nutrition intervention may have led to improved management of her metabolic complications.

Introduction

The pancreas has two types of glands: exocrine and endocrine. Most pancreatic cancers are diagnosed within the exocrine glands, specifically within the pancreatic duct epithelium. Most are adenocarcinomas and are found in the head of the pancreas (1-3). Management of blood glucose and diabetes can become problematic if endocrine glands (i.e., islet of Langerhans) are affected due to altered release of insulin and/or glucagon.

According to the American Cancer Society (ACS), people in the United States have a one in seventy-eight lifetime risk of developing pancreatic cancer (2). Overall risk increases with age; is slightly higher for men; and can be associated with cigarette smoking, alcohol, obesity, physical inactivity, high-fat diets, and pre-existing diabetes (2-3). Overall prognosis and treatment of pancreatic cancer are based on the stage of disease, which can be determined by tumor size, cell differentiation, and presence of metastasis. At this time, the overall five-year survival rate among patients with pancreatic cancer is less than six percent (2-4). Higher five-year survival rates of 18% to 24% are typically associated with small pancreatic cancers (less than two cm) that are localized and without regional lymph node involvement (5).

While risk of pancreatic cancer among those with long-standing diabetes is modestly elevated, older individuals newly diagnosed with diabetes have an eight-fold greater risk of pancreatic cancer when compared to the general population (6). Whether pancreatic cancer cells increase the risk for diabetes or diabetes increases the risk for pancreatic cancer is debatable, but studies now suggest that most pancreatic cancer-associated cases of diabetes occur within two–years prior to pancreatic cancer diagnosis. There is some evidence that in a small number of patients, glucose tolerance and/or diabetic status improves following pancreatic tumor resection, suggesting that the disease may be responsible for the diabetes (6).

Depending on disease status at presentation, treatment methods for pancreatic cancer can include surgery, which has the best chance of a cure. Pancreatoduodenectomy or Whipple procedure is the most common curative surgery for pancreatic cancer. This complex surgery removes the head of the pancreas, sometimes the body of the pancreas, the gallbladder, and part of the stomach, small intestine, and common bile duct. The remaining bile duct is connected to the small intestine, allowing bile to flow from the liver to the intestines (2). Unfortunately, most patients are ineligible for surgery when diagnosed (2-3,5-6) due to advanced disease at presentation. Early detection is key to improved outcome; tumor location (e.g., involvement of veins or arteries) will also impact outcomes.

The following case study involves a woman who presents 7.5 years after diagnosis of pancreatic cancer and whose initial treatment was the Whipple procedure.

Initial Diagnosis

RM, a previously healthy 57-year-old Caucasian female, was diagnosed in September 2005 with adenocarcinoma of the pancreas. Presenting tumor size was 3.0 x 3.9 cm and presenting symptoms included highly colored urine, light-colored stool, and progressive weight loss (some of which was intentional but out of proportion to the patient's efforts). The cancer was staged at T3N0M0. See Table 1 for Tumor Node Metastasis (TNM) classification.

Clinical History and Anthropometrics at Time of Initial Diagnosis (2005)

<u>Past Medical History</u>

- Thymus radiation at 6 months of age due to enlarged thymus, which was pressing on the patient's airway
- Tobacco use: one-half pack per day over 25 years and smoking-related chronic obstructive pulmonary disease (COPD)
- Hypertension

- Medications: Ibuprofen
- Allergies: Sulfa drugs, ondansetron (Zofran ®), and granisetron (Kytril ®)

Past Surgical History

- Three cesarean sections
- Tonsillectomy

Anthropometrics

- Height: 64 inches (162.5 cm)
- Weight: 162.8 pounds (lb) (74 kg)
- Usual Body Weight 212.8 lg (96.7 kg)
- Ideal Body Weight: 120 lb (54.5 kg)
- % Ideal Body Weight: 136%
- Adjusted Body Weight: 132 lb (60 kg)
- BMI: 28.0 (overweight range)

Approximately 80% of pancreatic cancer patients present with significant weight loss and cachexia (9). RM lost approximately 50 lb (27% of body weight) over a 6- to 8-month period before diagnosis that was related to intended weight loss as well as loss of appetite due to early satiety. She also experienced vomiting, discomfort in the upper left quadrant after meals, progressive body aches, and yellowish eyes and facial skin.

A Computed Tomography (CT) scan showed a tumor at the head of the pancreas that was pressing against the second part of the duodenum. It also showed dilation of the pancreatic duct, intrahepatic bile duct, and the portal vein; there was no evidence of metastasis.

Table 1. Summary of the TNM Tumor Classification System (7-8)

Classification Criteria	Grade	Definition
Primary Tumor (T)	TX	Tumor cannot be evaluated
	0T	No evidence of tumor
	TIs	Carcinoma in situ (CIS); abnormal cells are found but have not spread to neighboring tissues. CIS is not considered a cancer but may become a cancer
	T1	Tumor not palpable or visible by imaging
	T2	Tumor confined to primary cancer site
	T3	Tumor has spread to neighboring tissue
	T4	Tumor has metastasized
Lymph Nodes (N)	Nx	Regional lymph nodes cannot be evaluated
	N0	No regional lymph node involvement
	N 1,2,3	Regional lymph nodes involved; number reflects the number of nodes affected or extent of metastasis
Distant Metastasis (M)	MX	Distant metastasis cannot be evaluated
	M0	No distant metastasis
	M1	Distant metastasis is present

Chronology of Initial Treatment

September 2005

After being diagnosed, RM underwent concurrent chemotherapy with gemcitabine and cisplatin, and radiation over 25 fractions at 4,500 cGy. Tumor response was poor. RM developed a vitamin B12 deficiency which was treated with monthly vitamin B12 injections. Due to pancreatic insufficiency, as evidenced by diarrhea, RM was prescribed pancrelipase (Creon®), 1 tablet with each meal.

January 2006

RM underwent an exploratory laparotomy followed by a Whipple procedure with placement of a feeding jejunostomy. Post-operatively, RM developed hyperglycemia and was prescribed five units of glargine (Lantus®) subcutaneously at bedtime. RM was encouraged to follow a postgastrectomy diet consisting of six small, low-fat, high-protein, low-refined carbohydrate meals per day, and also continued to receive tube feedings until March 2006, when it was determined that oral diet tolerance was adequate. However, RM had severe weight loss post-treatment of 19.8 lb or 12% of initial weight. Serum albumin (2.8 g/dL) and pre-albumin (10 mg/dL) were below the normal range, reflecting inflammation due to treatment, weight loss, and loss of lean body mass.

While receiving tube feeding, RM's fasting blood glucose values ranged between 94 and 120 mg/dL, and 1-hour postprandial blood glucose values ranged between 113 and 120 mg/dL, indicating acceptable glucose control. Once the feeding tube was removed and oral intake increased, fasting glucose values increased to 120 to 160 mg/dL. RM was diagnosed with type 2 diabetes mellitus and she continued to receive five units of Lantus® long-acting insulin (subcutaneously) at bedtime. RM was referred to a Certified Diabetes Educator (CDE) for diabetes education, including carbohydrate counting, but did not meet with a CDE until 2011, or five years after referral.

March-August 2006

RM underwent six cycles of postoperative chemotherapy with Gemzar (Gemcitabine®), accompanied by dexamethasone (Decadron®). However, treatment was discontinued after four cycles because of adverse effects that led to a poor quality of life. Insulin injections were discontinued because of ecchymosis. Nateglinide (Starlix®) was prescribed to manage RM's blood glucose level; it was discontinued in late 2006. RM continued to take Pancrelipase (Creon®), Pantoprazole (Protonix®), and aspirin and to receive weekly injections of erythropoietin alfa (Procrit®).

August 2006-2011

According to RM, her blood glucose values remained within the normal range from approximately 2009 and 2012, with hemoglobin A1C (A1C) levels of 5.1% to 5.5%. In March 2012, A1C level increased to 7.9%. RM's cancer showed no metabolic activity. She began taking Ibandronate (Boniva®) and Zoledronic Acid (Reclast®) for osteoporosis as well as folic acid, calcium, and vitamin D supplements.

(Continued on next page)

Metastatic Disease

Metastasis to the lung was diagnosed in March 2012, and RM participated in a clinical trial in which she received a T-cell-activating drug targeted to the primary tumor. She was removed from the study because of a left pleural effusion and metastases to the liver.

Anthropometrics March 2012

- Height: 64 in (162.5 cm)
- Weight: 162.2 lb (73.7 kg) (stable with initial 2005 weight)
- % Ideal Body Weight: 135%
- Adjusted Body Weight: 132 lb (60 kg)
- BMI: 27.9 (overweight status)

While RM gained weight while in remission, she lost weight prior to being diagnosed with metastatic disease. RM's weight in March 2012 was consistent with her weight at the time of RM's initial diagnosis in 2005.

Approximately 3 months before beginning treatment for metastatic pancreatic cancer, RM met with a RD/CDE, who taught her carbohydrate counting. For three months RM met with the RD/CDE to review glucose management via carbohydrate counting. During this time RM also met with an RN/CDE to discuss insulin management. Once RM began treatment for metastatic pancreatic cancer, she decided to be followed by the oncology RD and her endocrinologist.

In March 2012, RM began treatment for her metastatic pancreatic cancer with a FOLFIRINOX chemotherapy regimen. Table 2 provides relevant laboratory values when initially diagnosed and during therapy in 2012. RM received more than 20 medications during the 2012 treatment period, which are listed in Table 3.

When initially diagnosed with pancreatic cancer, carcinoembryonic antigen (CEA) values were elevated, consistent with the presence of cancer. Total and direct bilirubin concentrations also were elevated, indicating abnormal liver function. Increased vitamin B12 values also could have reflected abnormal liver function, and decreased 25-hydroxyvitamin D values reflected insufficiency. An A1C value of 5.9% was indicative of pre-diabetes.

Table 2. Laboratory Values at Initial Diagnosis, During Therapy, and at Time of Treatment of Metastatic Disease

Laboratory Measure	Reference Value	2005 Laboratory Values	2012 Laboratory Values*	Range During Therapy
Carcinoembryonic Antigen	0.0-5.0 ng/mL	10.0 ng/mL	8.1 ng/mL ↑	2.0-81.2 ng/mL
CA-19-9**	0-37 U/mL	<1 U/mL	<1 U/mL	<1-37 U/mL
Hemoglobin	3.6-11.0 g/dL	9.6 g/dL	10.4 g/dL ↑	8.0-13.9 g/dL
Hematocrit	35.0%-47.0%	44.8%	31.5% ↑	24.8%-44.8%
Platelets	150-440 K/uL	210 K/uL	82 K/uL ↓	262-255 K/uL
Neutrophils	46%-79%	75.5%	72.9%	36.8%-89%
Glucose		155 mg/dL	324 mg/dL	54-592 mg/dL
Total Bilirubin	0.4-1.4 mg/dL	10.1 mg/dL	0.7 mg/dL	0.4-10.1 mg/dL
Direct Bilirubin	0.2-0.2 mg/dL	6.6 mg/dL	0.1 mg/dL	0.1-6.6 mg/dL
Amylase	28-100 U/L	36 U/L	52 U/L	30-108 U/L
Lipase	22-51 U/L	23 U/L	12 U/L	8-23 U/L
Albumin	3.8-5.3 g/dL	3.9 g/dL	3.9 g/dL	1.6-4.2 g/dL
Prealbumin	18-45 mg/dL	25 mg/dL	18 mg/dL	7-25 mg/dL
Vitamin B-12	>200 pg/mL = acceptable***	778 pg/mL	1,174 pg/mL	227-117 pg/mL
Glycated Hemoglobin A1C	4.4%-6.4%	5.9%	7.9%	5.1%-7.9%
25-hydroxyvitamin D	30-80 ng/mL	22 ng/mL	30 ng/mL	19-30 ng/mL

*Arrows reflect trend.

**CA 19-9 radioimmunoassay test measures the concentration of tumor-associated antigens in the serum of persons with pancreatic cancer.

***According to World Health Organization criteria.

Over this period of time the RD consulted with RM at least weekly due to continued elevated blood sugars, frequent bouts of diarrhea and weight loss.

Nutrition

In March 2012, an RD was consulted to assist RM with management of elevated blood glucose, frequent bouts of diarrhea, and weight loss.

RM's diet consisted of high-fat, high-refined carbohydrate foods, with three meals and two to three snacks per day. RM also consumed a daily Greek yogurt to replete gut flora. RM drank limited amounts of alcohol on occasion and adequate amounts of fluid. A typical day's intake consisted of the following:

Breakfast: Two to three caffeinated coffees (with milk only) on waking. About 60 minutes later RM ate either a large bagel with butter or, on most days, an egg, bacon and cheese breakfast sandwich (3-4 carbs).

RM stated her blood sugar level was very sensitive to caffeine, and drinking caffeinated beverages would result in a 40-80 point increase in blood sugar level.

(Continued on page 32)

Table 3. Medications Provided During 2012 Treatment (10)

Medication	Mode of Action	Nutrition-Related Adverse Effects
Levothyroxine (Synthroid®)	Replacement for low thyroid hormone	Weight loss, increased hunger, and diarrhea (all infrequent)
Glargine (Lantus®)	Long-acting injectable insulin	Hypoglycemia
Nateglinide (Starlix®)	Oral insulin-secretagogue	Hypoglycemia, weight gain
Detemir (Levemir®)	Long-acting insulin analog	Hypoglycemia
Lispro (Humalog®)	Rapid-acting insulin analog	Hypoglycemia, weight gain
Gemzar (Gemcitabine®)	Antimetabolite chemotherapy to slow or stop cancer cell growth	Loss of appetite, mouth sores, nausea, vomiting, diarrhea, constipation
FOLFIRINOX Therapy		
5-Fluorouracil (5-FU)	Antimetabolite, inhibits DNA repair	Severe mucositis Esophagitis Taste alterations Decreased appetite
Leucovorin (Folinic Acid®)	Chemotherapy enhancer or protectant	Avoid pyroxidine supplements Rare nausea/vomiting
Irinotecan (Camptosar®)	Plant alkaloid; DNA replication inhibitor/cytotoxin	Severe nausea/vomiting/ diarrhea/anorexia
Oxaliplatin (Eloxatin®)	Platinum-based alkylating agent, breaks DNA helix strand, interfering with DNA replication	Nausea/vomiting/diarrhea/mouth sores/anorexia Avoid consuming cold drinks and foods Can cause hyperglycemia due to 5% dextrose used as the carrier for administration
Lorazepam (Ativan®)	Antianxiety agent	Nausea, constipation, change in appetite
Metronidazole (Flalgyl®)	Antibiotic to treat bacterial and protozoal infections	Diarrhea, nausea, stomach pain, loss of appetite, constipation, changes in taste, and dry mouth.
Epoetin alfa (Procrit®)	Treatment for anemia related to myelosuppressive chemotherapy	None
Pegfilgrastim (Neulasta®)	Colony-stimulating factor; regulates production of neutrophils	Nausea/vomiting
Dexamethasone (Decadron®)	Glucocorticosteroid anti-inflammatory agent	Increased appetite, nausea, hyperglycemia
Aprepitant (Emend®)	Antiemetic	Nausea, constipation, diarrhea, loss of appetite
Palonosetron hydrochloride (Aloxi®)	Antinausea injection given day of chemotherapy	Constipation
Oxycodone hydrochloride (Oxycontin®)	Time-release pain narcotic	Constipation
Lisinopril (Prinivil®, Zestril®)	Angiotensin-converting enzyme inhibitor for high blood pressure	Avoid salt substitutes and potassium supplements Maintain hydration
Pancrelipase (Creon®)	Pancreatic enzyme replacement	Monitor for pork allergies. Hyper- and hypoglycemia. Maintain awareness of cultures that do not consume pork
Prochlorperazine (Compazine®)	Antinausea	None
Ibandronate sodium (Boniva®)	Bisphosphonate for osteoporosis	Reflux, esophageal discomfort
Zoledronic acid (Reclast®)	Bisphosphonate for osteoporosis	Nausea, vomiting, diarrhea within 3 days of treatment
Pantoprazole (Protonix®)	Proton pump inhibitor	Can cause vitamin B-12 deficiency
Multivitamin		Dyspepsia
Aspirin		Dyspepsis
Calcium		
Folic Acid		
Vitamin D		

Lunch usually consisted of a sandwich/ grinder, a salad, pizza, or a full meal of protein, starch and vegetable or pasta (3-5 carbs).

Dinner often included foods such as a pulled-pork sandwich or a full meal as described above (3-5 carbs).

Snacks: On most days RM snacked quite heavily in the afternoon and evening. Her snacks usually consisted of fruit, chocolate, chips, nuts, ice cream, candy, and pastries (2-6 carbs).

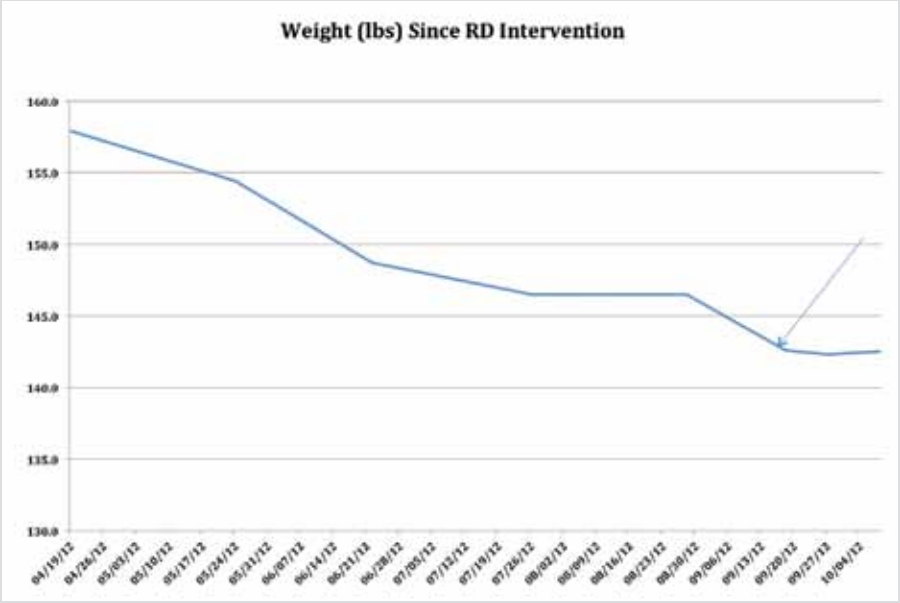
Due to rapid weight loss, the RD advised RM to increase energy intake from all sources and to keep carbohydrate intake consistent. The RD recommended increased protein and higher fat foods as tolerated.

The initial goal was to stabilize weight via a liberalized diet (rather than a strict carbohydrate controlled diet) while managing blood glucose levels and diarrhea with medication. RM continued to lose weight and suffer from diarrhea, and so nutrition intervention was modified. RM was encouraged to increase her protein intake, especially on the days of treatment and the subsequent 2 days to help mitigate the effect of the corticosteroids. RM was also advised to moderate intake of carbohydrate, in particular refined carbohydrate foods, while keeping total carbohydrate intake consistent. RM was also advised to moderate her fat intake, and to consume a variety of foods consistent with standard nutrition recommendations for diabetes (11). However, RM was not compliant with these recommendations and consumed a high-fat, high-carbohydrate diet that included many foods high in sugar.

RM's weight loss continued until the RD recommended an increase in pancrelipase (Creon®) dose, from 5-6 capsules daily to 9 capsules daily; pancreatic enzymes were taken with meals and snacks. Figure 1 diagrams RM's weight history.

When RM was initially diagnosed with pancreatic cancer in 2005, her A1C level was

Figure 1. RM's weight changes during the period of nutrition intervention.



Arrow represents the point at which the Pancrelipase (Creon®) dose was increased.

5.9%, which was within the range of 5.7-6.4% indicative of risk for diabetes (or pre-diabetes). Between March and November 2012, RM's A1C readings were elevated at around 7.8%. Factors influencing elevated A1C levels included restarting chemotherapy with FOLFIRINOX, which required administration of a corticosteroid (Decadron®) and Dextrose 5%, which was used as a carrier for one of the chemotherapeutic agents (Oxaliplatin/ Eloxatin®). RM's insulin regimen was adjusted multiple times throughout treatment (Table 4), primarily based on hyperglycemia resulting from corticosteroid administration. However, RM was noncompliant with recommendations for mealtime insulin due to fear of hypoglycemia. No pattern was exhibited on the Continuous Glucose Monitor printouts to indicate potential regular points of adjustments. Essentially, RM administered random doses of insulin based on postprandial fingerstick blood sugar values and sometimes on Continuous Glucose Monitor readings. The result was that she was "chasing" blood glucose values, which resulted in occasional hypoglycemia.

Discussion and Insight

Nutrition intervention addressed weight loss related to multiple bouts of diarrhea, inadequate oral intake during treatment, and elevated blood glucose values. Over the course of treatment, these challenges were exacerbated by the patient's inability to adhere to nutrition recommendations; adjust her insulin regimen; and maintain a consistent carbohydrate intake. On some days, debilitating fatigue was likely a contributing factor, preventing RM from preparing nutritious meals and following nutrition recommendations. RM also was fearful of hypoglycemia, which prevented her from following the endocrinologist's insulin recommendations. The patient lived alone, although she reported having a supportive family and friends. The primary nutrition goal was stopping weight loss; this was achieved following improved management of diarrhea with appropriate enzyme replacement. In August 2012, the RD recommended increasing RM's Pancrelipase (Creon®) dose from 5 to 6 capsules daily to a therapeutic dose of 9 capsules daily. Following this change, her diarrhea and malabsorption resolved, weight stabilized, and energy level increased.

During the FOLFIRINOX chemotherapy regimen, RM was fearful of low blood glucose levels and of using insulin (Lispro/

Table 4. Insulin Regimen

Date	Insulin Detemir (units)		Insulin Lispro (units/g of carbohydrate ratio or total units at meal)			Correction Factor or Sliding Scale
	AM	PM	Breakfast	Lunch	Dinner	
3/15/12	10	10	1 U/7 g	1 U/8 g	1 U/7 g	1:40 (add 1 U for every 40 points above target)
3/21/12	12	10	1 U/5 g	1 U/6 g	1 U/6 g	
4/09/12	20	16	1 U/7 g	1 U/7 g	1 U/7 g	
4/10/12*	20	21	1 U/3 g	1 U/3 g	1 U/3 g	1:20 (add 1 U for every 20 points above target)
5/07/12	?	?	2	2	2	
5/24/12	16	8	2	2	2	
5/30/12**	16	8	9	8	8	6 U if blood glucose 150-200 mg/dL
						8 U if blood glucose >201 mg/dL
8/09/12	16	8	2	2	2	4 U at end of meal (if high-fat meal)
8/23/12	16	8	2	2	2	4 U at end of meal (if high-fat meal)
9/27/12	18	8	5-6	5-6	5-6	

*This regimen is ONLY for days of chemotherapy with the administration of corticosteroids.

**New regimen is ONLY for days of chemotherapy with the administration of corticosteroids.

Humalog®). RM's endocrinologist believed she was producing inconsistent amounts of endogenous insulin, which complicated glycemic control. On some days RM did not use any rapid-acting insulin for fear of hypoglycemia, resulting in extremely elevated blood glucose values. Blood glucose levels ranged from 30 to greater than 500 mg/dL ("High" - meter unable to read) and interfered with her ability to stabilize and gain weight.

During treatment, RM also stopped measuring the insulin-to-carbohydrate ratio and using sliding scale insulin estimates because of her fear of hypoglycemia. RM's Continuous Glucose Monitor would alarm at 200 mg/dL for ascending blood glucose and 80 mg/dL for descending blood glucose, but she still experienced lows. RM attributed these lows to rapid drops in her blood glucose, which per the endocrinologist was possibly due to endogenous insulin production. RM was asked to increase her alarm setting to 100 mg/dL, but no change was made. RM's response to multiple suggestions from the medical team was, "I know my body and I know what I feel I need when I need it." Lack of adherence to recommendations resulted in an elevated A1C of 7.9% and a fructosamine value of 432 umol/L, indicative of overall poor glycemic control.

Approximately three months following treatment, the patient returned to the CDE (an RD) who discovered that RM was basing pre-meal insulin administration on the reading from the Continuous Glucose Monitor rather than fingerstick readings. The Continuous Glucose Monitor reads the glucose content of interstitial fluid, while a glucose meter uses capillary blood glucose, which is the more reliable reading, especially as a basis for pre-meal insulin doses. While RM was instructed to use fingerstick blood glucose readings to determine pre-meal insulin, she did not use her fingerstick values to dose insulin. Although RM monitored fingersticks multiple times daily, she did not use this information for insulin dosing.

Conclusion

Outcomes

- Diarrhea resolved after increasing Pancrelipase (Creon®) dose
- Weight stabilized after diarrhea resolved
  - Blood glucose control remained volatile and difficult to manage:
  - Blood glucose in early October 2012: 63 to 367 mg/dL
  - Blood glucose in mid-November 2012: 62-401 mg/dL
- RM requested a referral to the RD/CDE to discuss use of an insulin pump
- RM's endocrinologist continued to work with her
- RM's reticence or inability to follow consistent carbohydrate counting, insulin-to-carbohydrate ratios/ correction factors, and insulin adjustments resulted from a fear of hypoglycemia.
- At future follow-up visits to the cancer center, the RD planned to revisit the insulin-to-carbohydrate ratio/correction factors and proper blood glucose monitoring technique in collaboration with the RD/CDE
- Malabsorption and weight would be continually monitored and assessed at each visit

The medical team explored additional treatment options including clinical trials for pancreatic cancer sponsored by the National Institutes of Health, but RM was not eligible due to stable disease.

Deborah S. Downes, RD, CSO, CD-N, is an Oncology Dietitian at The NEAG Cancer Center, Sodexo at UCONN Health Center Farmington, CT 06030

Ms Downes would like to thank Amy DiCioccio, RD, CSO, CD-N, for her contributions to this article.

(Continued on next page)

References

1. Bose D, Katz MHG, Fleming JB. Pancreatic Adenocarcinoma. In: Feig BW, Berger DH, Fuhrman GM, eds. *In The MD Anderson Surgical Oncology Handbook*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:368.
2. American Cancer Society. *Pancreatic Cancer Overview.* 2013. http://www.cancer.org/cancer/pancreaticcancer/overviewguide/pancreatic-cancer-overview-what-is-cancer. Accessed April 2013.
3. Pancreatic Cancer Action Network website. http://www.pancan.org/section_facing_pancreatic_cancer/learn_about_pan_cancer/diet_and_nutrition/Diabetes.php. Accessed November 2012.
4. Li J, Cao G, Ma Q, Liu H, Li W, Han L. The bidirectional interaction between pancreatic cancer and diabetes. *World J Surg Oncol.* 2012;10:171.
5. National Cancer Institute. Pancreatic Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/pancreatic/HealthProfessional/page1/AllPages/Print Last Modified 2/14/13. Accessed 5-5-13.
6. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol.* 2009;10(1):88-95.
7. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer; 2002.
8. Staging of cancer of the pancreas. Cancer of the Pancreas Task Force. *Cancer*. 1981;47(6 suppl):1631-1639.
9. Ferrucci LM, Bell D, Thornton J, et al. Nutritional status of patients with locally advanced pancreatic cancer. *Support Care Cancer.* 2011;19(11):1729-1734.
10. Drug Information Online. Drug Index A to Z. http://www.drugs.com/drug_information.html Updated 2013. Accessed April 10, 2013.
11. American Diabetes Association. Standards of medical care in diabetes 2012. *Diabetes Care.* 2012;35(suppl 1):S11-S63.

2012-2013 Oncology Nutrition DPG Officers and Committee Chairs

(* Voting member)

Chair*
Suzanne Dixon, MPH, MS, RD
Phone (C): 503-313-5202
Email: sdixon@umich.edu

Chair-elect*
Elaine Trujillo, MS, RD
Phone (W): 301-594-0903
Email: trujille@mail.nih.gov, elainebtrujillo@hotmail.com

Secretary*
Kelay Trentham, MS, RD, CSO, CD
Phone (W): 253-403-3298
Email: kelayt@gmail.com

Treasurer*
Andreea Nguyen, MS, RD, CSO, LD, CNSC
Phone: (W): 214-820-2005
Email: andreea.nguyen@baylorhealth.edu

Past Chair*
Denise C Snyder, MS, RD, CSO, LDN
Phone (W): 919-660-7580 (preferred)
Email: denise.snyder@duke.edu

Nominating Committee Chair*
Katie Harper, MS, RD, CSO
Phone (C): 425-894-8065
Email: katie.harper@uch.edu

Western Area Representative
(CA, TX, AZ, NM, WA, OR, NV, WY, ND, SD, HI, AK, ID, MT, UT, CO, Asia, NZ, AU)
Amy Patton, RD, CSO, CNSD
Phone (W): 702-947-0286
Email: amypattonrd@hotmail.com

Eastern Area Representative
(VA, GA, PA, DE, NH, RI, NC, SC, NY, FL, NJ, MD, VT, ME, MA, DC, PR, and Europe)
Karen Pasquazzi, RD, CSO, LDN
Phone (W): 401-444-6602
Phone (H): 401-946-9644
Email: kpas7@cox.net

Central Area Representative
(MI, IN,AR, AL, IA, KS, OH, KY, MO, MS, MN, OK, WV, TN, LA, IL, WI, NE and Canada)
Chandy Lockman Hoke, MS, RD, CSO, LMNT
Phone: (pager): 402-221-5009
Email: chandyhoke@yahoo.com, chandy.hoke@me.com

Development Coordinator
Kristin Ringo, RD, CSO, LD, CNSC
Phone (W): 214-820-7745
Email: kristhal@baylorhealth.edu

Account Manager
Louise Chen, RD, LD, CNSC
Phone (W): 214-865-1645
Email: LouiseLChen@gmail.com

Alliance Coordinator
Rhone M. Levin, MEd, RD, CSO, LD
Phone (W): 208-706-4170
Email: uwgirl@aol.com, levinr@slhs.org

Electronic Mailing List (EML) Administrator
Dianne Kiyomoto, RD, CSO
Phone (H): 559-431-9728
Email: diannerd79@yahoo.com

Membership Chair
Alison Ryan, MS, RD, CSO, CNSC
Phone (C): 415-627-8122
Email: alison.n.ryan@gmail.com

Academy Representative to CoC
Kathryn Hamilton, MA, RD, CSO, CDN
Phone (C): 201-669-6856
Email: kathryn.hamilton@verizon.net, kathryn.hamilton@atlantichealth.org

Awards Co-Chair
Tricia Cox, MS, RD, LD, CNSC
Phone (C): 903 436-2108
Email: tricia.melhart@baylorhealth.edu

Oncology Nutrition Connection
Newsletter Editor
Maureen Leser, MS, RD, CSO, LD
Phone: (H) 410-208-9120
Email: mgoreleser@gmail.com

Associate Editors
Maureen Boswell, RD, CSO, CDE
Phone: 509-860-7214
Email: Maureen_8@hotmail.com

Alicia Merritt, MS, RD, CSO, CNSC, LD
Phone: 713-791-1414 X4650
Email: aliciard12@gmail.com

Jocylene O'Brien, MPH, RD, CSO, CNSC, LDN
Phone (W): 781-756-2228
Phone (C): 617-549-8826
jocelynenasser@yahoo.com

Continuing Education Chair
Maureen B. Huhmann, DCN, RD, CSO
Phone (W): 973-765-1514
Email: maureen.huhmann@us.nestle.com

Public Policy & Reimbursement Chair
Nicole Fox, RD, LMNT, CNSC
Phone (W): 402-559-6808
Email: nfox@nebraskamed.com

House of Delegates ONDPG Delegate
Katrina Claghorn, MS, RD, CSO, LDN
Phone (W): 215-615-0538
Email: katrina.claghorn@uphs.upenn.edu

Website Administrator
Heather Bell-Temin, MS, RD, CSO, LDN
Phone (W): 813-745-6189
Email: heather.bell-temin@moffitt.org

Website Assistant
Maranda Robison
Phone (C): 720-254-0425
Email: maranda.robison@gmail.com

Social Media Coordinator
Maureen Gardner, MA, RD, CSO, LDN
Phone (W): 813-745-2875
Email: maureen.gardner@moffitt.org

EBlast Coordinator
Kristen Lange, MS, RD, CSO, LD/N
Phone (W): 813-745-1314
Email: kristen.lange@moffitt.org

2012-2013 DCE Officer Directory

EXECUTIVE COMMITTEE

Chair
Andrea Dunn, RD, LD, CDE
440-871-1421
dm2rdcde@gmail.com

Chair-Elect
Lisa Brown, RD, LD, CDE
612-889-5633
brown1457@gmail.com

Past Chair/Industry Relations Chair
Amy Hess Fischl, MS, RD, LD, BC-ADM, CDE
847-528-2804
AmyFish12@aol.com

Secretary
Ann Constance, MA, RD, CDE
906-361-9754
Ann.constance@yahoo.com

Treasurer
Amber Wamhoff, MA, RD, LD, CDE
314-583-4525
wamber470@yahoo.com

Membership Coordinator
Carolyn Harrington, RD, CD, CDE
941-882-3071
carolyn.harrington217@ymail.com

Print Communications Coordinator
Liz Quintana, EdD, RD, LD, CDE
304-293-7246
equintana@hsc.wvu.edu

Electronic Communications Coordinator
Betty Krauss, RD, CDE
616-242-0494
betty.krauss@maryfreebed.com
bkmda@aol.com

Professional Development Coordinator
Susan Rizzo, RD, LDN, CDE
847-352-2035
Nutrizz6RD@comcast.net

Public Policy
Susan Yake, RD, CD, CDE, CLC
360-475-4681
yakes36@bigplanet.com
susan.yake@med.navy.mil

Research Coordinator
Maria Chondronikola, MS, RD
646-244-2920
Chondronikola@gmail.com

Dietetic Practice Group Delegate
Maryann Meade, MS, RD, CDN, CDE
203-265-9756
mameade@sbcglobal.net

Nominating Committee Chair
Carol Hamersky, MBA, CDE, RD
609-216-3112
cmhamersky@comcast.net

NEWSLETTER COMMITTEE

***News*FLASH Editor**
Lorena Drago, MS, RD, CDN, CDE
718-263-3926
lorenamsrd@aol.com

***OTCE* Editor**
Diane Reader, RD, CDE
952-993-3840
Diane.Reader@ParkNicollet.com

***OTCE* Associate Editor**
Sue McLaughlin, MOL, RD, LMNT, CDE
402-397-7280
Smclau8303@aol.com

ELECTRONICS COMMITTEE

e-Update Editor
Deborah Ting, RD
206-518-3556
robotschmobot@hotmail.com

Website Editor
Laura Russell, MA, RD, CDE
701-390-9541
lcruss58@gmail.com

Web Site Monitor
Sherri T. Isaak, MS, RD, BC-ADM, CDE
isaakrd@yahoo.com

Listserv Moderator
Marylou Anderson, MS, RD, CD, CDE
253-572-9175
fourcats2001@msn.com

COMMITTEE CHAIRS

Alliance/International
Amy Hess Fischl, MS, RD, LD, BC-ADM, CDE
Lisa Brown, RD, LD, CDE
Andrea Dunn, RD, LD, CDE

Awards Committee Chair
Nell Stuart, MS, RD, LD, CDE
304-276-3785
nellsloverstuart@gmail.com

Awards Committee Assistant Chair
Johann Burani, MS, RD, CDE
973-538-1101
jburani@gmail.com

Publications Committee Chair
Naomi Wedel, MS, RD, CD, BC-ADM, CDE
608-630-0983
naomi.wedel@gmail.com

Mentor Program Chair
Pat Severson-Wager, MS, RD, CDN, CDE
518-674-8213
Preaw1234@aol.com

Reimbursement Committee Chair
Marla Solomon, RD, LD/N, CDE
773-753-1313
marla@mcsolomon.com

SPECIAL PROJECT HEADS

National Diabetes Education Program/ NDEP Liaison
Ann Constance, MA, RD, CDE
906-361-9754
ann@diabetesmichigan.org

Technology Task Force Chair
Jill Richards-Divita, RD, LD, CPT, CDE
440-429-4175
jillrdcde@gmail.com

MEMBERSHIP COMMITTEE

Membership Representatives
Janice Friswold, RD, LD, CDE
216-844-1058
janice.friswold@uhhospitals.org

Joann K. Rinker, MS, RD, LDN, CDE
704-985-0624
Joanne.Rinker@dhhs.nc.gov

Marsha Martin Lewis, MPH, RD, LD, CDE
478-405-6422
lewispmt@cox.net

Social Media Chair
Jennifer Hyman, MS, RD, CDN, CDE
516-570-0758
jenlhyman@gmail.com

Social Media Committee
Constance Brown-Riggs, MSEd, RD, CDN, CDE
516-795-4288
constance@eatingsoulfully.com

Dawn Noe, RD, LD, CDE
937-903-2321
dawn.noe@gmail.com

ACADEMY/DCE STAFF

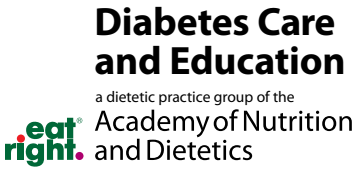
Administrative Manager
Linda Flanagan Vahl
312-899-4725
800-877-1600 ext 4725
Fax: 312-899-5354
lflanagan@eatright.org

DCE SUPPORT SERVICES

DCE Webmaster
Aurimas Adomavicius
aurimas@devbridge.com

DCE Web Address
www.dce.org

DCE Copy Editor
Deb Kuhlman
dkedits@speakeasy.net


Diabetes Care
and Education
a dietetic practice group of the
Academy of Nutrition
and Dietetics


Oncology
Nutrition
a dietetic practice group of the
Academy of Nutrition
and Dietetics