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Review

Communicating clinical research to reduce cancer risk through diet: Walnuts as a case example

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ABSTRACT: Inflammation is one mechanism through which cancer is initiated and progresses, and is implicated in the etiology of other conditions that affect cancer risk and prognosis, such as type 2 diabetes, cardiovascular disease, and visceral obesity. Emerging human evidence, primarily epidemiological, suggests that walnuts impact risk of these chronic diseases via inflammation. The published literature documents associations between walnut consumption and reduced risk of cancer, and mortality from cancer, diabetes, and cardiovascular disease, particularly within the context of the Mediterranean Diet. While encouraging, follow-up in human intervention trials is needed to better elucidate any potential cancer prevention effect of walnuts, per se. In humans, the far-reaching positive effects of a plant-based diet that includes walnuts may be the most critical message for the public. Indeed, appropriate translation of nutrition research is essential for facilitating healthful consumer dietary behavior. This paper will explore the translation and application of human evidence regarding connections with cancer and biomarkers of inflammation to the development of dietary guidance for the public and individualized dietary advice. Strategies for encouraging dietary patterns that may reduce cancer risk will be explored.

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INTRODUCTION

The connection between diet and cancer has been well-established, as affirmed by the considerable international consistency among dietary and lifestyle recommendations for reducing risk of cancer and other chronic diseases. The World Cancer Research Fund (WCRF), American Institute for Cancer Research (AICR) and the American Cancer Society guidance each emphasize a plant-based diet, a physically active lifestyle, limited alcohol, and maintaining a healthy weight [1,2].

Dietary recommendations such as those issued by the World Health Organization are remarkably consistent with cancer risk reduction guidance, particularly in emphasizing the importance of dietary pattern over individuals foods, a plant-based dietary pattern, maintaining a healthy weight, and physical activity [3]. There is a broader focus on chronic disease risk, advising lower intake of saturated fats and higher intake of unsaturated fatty acids to reduce the risk of heart disease. However, even these differences may diminish over time as it is increasingly evident that cancer, heart disease, and diabetes share certain common mechanisms, including inflammation and oxidative stress, which are impacted by dietary fatty acids.

Inflammation is one mechanism through which cancer is initiated and progresses [4], and is implicated in the etiology of comorbidities, such as type 2 diabetes, cardiovascular disease, and visceral obesity [5-7]. Walnuts provide an informative example of an emerging area of research around diet, inflammation, and cancer. Complementary to the recent review of preclinical evidence for the impact of walnuts on cancer risk via inflammatory mechanisms [8], this paper will explore the human evidence for this relationship, how it may be incorporated appropriately into nutrition messages for the public and individuals, and strategies for facilitating related consumer behavior changes.

Evidence in Humans for Walnuts, Cancer, Inflammation, and Related Diseases

Walnuts and cancer

Numerous dietary components in walnuts may counter inflammation, thus certain cancers, including α-linolenic acid (ALA), ellagitannins, γ-tocopherol, melatonin, β-sitosterol, and fiber [8]. The evidence from *in vitro* and animal studies is increasingly supportive of a protective role for walnuts in inflammation-related cancer mechanisms [8-13].

Although there is variation in the nutritional profiles of tree nuts, few epidemiological studies consider walnuts separately from nuts. Still, such analyses provide a foundation for further study of the relationship between individual nuts and cancer prevention, and one analysis of the PREDIMED (Prevención con Dieta Mediterránea) cohort has begun to sort out the independent effects of walnuts [14]. For those who consumed

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> 3 servings walnuts/wk versus none over a median of 4.8 yr, the multivariate-adjusted HR for death from cancer was 0.46 (0.27-0.79, 95% CI, *P*-trend = 0.005).

Reduced risk of mortality from cancer with higher consumption of all nuts has also been observed. In the PREDIMED cohort, the multivariate-adjusted HR for death from cancer with > 3 versus 0 servings of nuts was 0.60 (0.37-0.98, *P*-trend = 0.064) [14]. A retrospective analysis of women in the Nurses' Health Study and men in the Health Professionals Follow-up Study revealed a multivariate-adjusted hazard ratio of 0.89 (0.81-0.99, 95% CI) for deaths from cancer, comparing a higher frequency of nut consumption at > 5 times/wk to 0 servings/wk (*P*-trend = 0.03) [15].

Consuming more than 2 versus 0 servings (28 g) of nuts/wk was associated with a 32% lower risk (0.48-0.96, 95% CI, *P*-trend = 0.01) of pancreatic cancer among women followed prospectively in the Nurse's Health Study [16]. Also, among the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, women, but not men, with the highest (> 6.2 g/d) versus lowest (0 g/d) intake of nuts and seeds had a 31% (0.50-0.95, 95% CI) lower risk of colon cancer [17]. No association was noted between nuts and total, lymphoid, and myeloid leukemias in the EPIC cohort, however [18].

Human clinical evidence directly assessing walnuts and cancer risk as a primary outcome is limited. There are two human clinical trials that have investigated the potential impact of walnut consumption on prostate health biomarkers that can be indicative of prostate cancer risk. In a randomized crossover study, 40 healthy middle-aged men consumed 35 g walnuts (12% total energy) per day for 6 months, then a control diet for 6 months with no effect on prostate-specific antigen (PSA) levels [19]. A randomized parallel trial with 21 men (45-75 y) at risk for prostate cancer (elevated PSA) examined the effects of a usual diet with or without walnuts (75 g/d) in place of any other source of dietary fat on markers of prostate and vascular health [20]. After 8 weeks, serum γ-tocopherol levels trended upwards (*P* = 0.08) in the walnut group, and the α-tocopherol to γ-tocopherol ratio decreased significantly (*P* = 0.01). There was no change in PSA, and a non-significant increase in the free to total PSA ratio (*P* = 0.07) in those consuming walnuts.

Walnuts and inflammation

Primary measures of the effect of walnuts on biomarkers of inflammation and oxidative stress are relevant due to the implications of chronic inflammation for cancer risk, and have been reviewed by others [21]. Walnuts have been studied within the context of the Mediterranean diet. In the 1-year, randomized PREDIMED (n = 516), adults consuming a Mediterranean diet with either extra virgin olive oil or mixed nuts (walnuts, almonds, and hazelnuts) versus a low fat diet had lower intercellular adhesion molecule-1 (ICAM-1), interleukin (IL)-6, tumor necrosis factor (TNF)R60, and TNFR80 levels (*P* < 0.05) [22]. Hypercholesterolemic men and women (n = 21) following a Mediterranean diet with walnuts replacing foods high in monounsaturated fatty acids (32% of energy) compared to a Mediterranean diet for 4 wk in a crossover randomized trial were found to have lower levels of vascular cell adhesion molecule-1 (VCAM-1) (*P* < 0.05), but similar levels of ICAM-1, C-reactive protein (CRP), homocysteine, and oxidation biomarkers [23]. Nuclear factor κB (NF-κB) level also was shown to decrease with a Mediterranean versus Western diet (*P* < 0.05), with no significant differences between the Mediterranean and high-ALA diet (walnuts were not specified in this study) [24].

Diets with increased ALA content from walnuts and other foods such as canola or flaxseed oils have also been studied with respect to inflammation [25]. Adults with high cholesterol (n = 23) were randomized to consume diets high in ALA (from walnuts, walnut oil, and flaxseed oil), high in linoleic acid (LA), or typical American diets. Decreased levels of IL-6, IL-1β and TNF-α production were observed in the ALA versus other diet groups (*P* < 0.05). In a later analysis of the data, the ALA diet was associated with lower CRP, VCAM-1, and E-selectin (*P* < 0.01) in comparison to the LA diet [26].

Walnuts have been compared to fish with respect to impact on markers of inflammation and endothelial activation in a randomized crossover trial with normal to mildly hyperlipidemic adults [27]. The three isoenergetic diets consumed for 4 wk were the walnut diet (1.8% of energy as n-3 fatty acids), the fish diet (0.8% of energy as n-3 fatty acids), and the control diet (0.4% of energy as n-3 fatty acids with no nuts or fish). The walnut diet inhibited E-selectin by 12.7% versus the fish diet. The fish diet inhibited ICAM-1 by 4.5% versus the control diet. Both the walnut and fish diets Inhibited prostaglandin E metabolite (PGEM) and 11-dehydro thromboxane B2, but had no effect on IL-1β, IL-6, TNF-α, CRP, or the number of circulating lymphocyte subsets.

Walnuts and other inflammation-related health conditions

Epidemiological evidence for walnuts specifically was noted in the PREDIMED cohort, where > 3 versus 0 servings walnuts/wk is associated with a multivariate-adjusted HR for death from cardiovascular disease of 0.53 (0.29-0.98 95% CI, *P*-trend = 0.047) [14]. For all nuts, multivariate-adjusted HR for death from cardiovascular disease was 0.45 (0.25 to 0.81, 95% CI, *P*-trend = 0.091) [9], and for risk of metabolic syndrome (HR = 0.74, 0.65-0.85 95% CI, *P*-trend < 0.001) with > 3 versus 0 servings/d [28]. A retrospective analysis of women in the Nurses' Health Study and men in the Health Professionals Follow-up Study revealed a multivariate-adjusted hazard ratio of 0.75 (0.62–0.84) for deaths from cardiovascular disease (*P*-trend < 0.001) with > 5 times/wk versus no nuts [15]. In addition walnuts were also associated with lower risk of diabetes in the Nurse's Health Study cohort (multivariable-adjusted HR = 0.85, 0.77-0.94, 95% CI, *P*-trend = 0.002) with 2 versus 0 servings/wk [29].

Human clinical evidence is also available with respect to nuts or walnuts and cardiovascular health. The primary outcome assessed in the PREDIMED trial was cardiovascular events. There was a 28% reduced risk for major cardiovascular events (0.54-0.96, 95% CI, *P* = 0.03) among subjects who were randomized to consume a Mediterranean diet with nuts, comparable to the 30% reduced risk (0.54-0.92, 95% CI, *P* = 0.01) among those who consumed a Mediterranean diet with extra-virgin olive oil [30]. In addition, two randomized crossover trials provided 56 g/d walnuts (2 servings) for 8 weeks versus an *ad libitum* diet. Endothelial function as measured by flow mediated dilation

(FMD) improved in overweight adults with at least one risk factor for metabolic syndrome (n = 46) ($P = 0.019$) [31] and in adults with diabetes (n = 24, $P = 0.04$) [32].

Implications of Walnut Evidence for Communications about Diet and Cancer

Public health messages have greater potential for positive impact when they are simple, specific, and action-oriented. Repetition is critical, and most effective when consistent messages are delivered by multiple credible sources. Why, then, do consistent recommendations from World Cancer Research Fund, American Cancer Society, World Health Organization, and others not result in widespread dietary behavior change?

While it is tempting to look first to the consumer, it is important to acknowledge that nutrition evidence continues to evolve. Inconsistencies between pre-clinical, epidemiological, and clinical evidence sometimes leave the research community confused and in disagreement. Carcinogenesis is unique to the body site in which is occurs, and the process spans many years, complicating and increasing the expense of large intervention trials. Other challenges in such research, for any health outcome, is that the overall dietary pattern is more than the sum of the individual foods or nutrients eaten, and there are both genetic and environmental factors that cause considerable variation in the impact of diet among individuals.

Taking walnuts as an example, preclinical evidence for a protective effect of walnuts against cancer is encouraging, but requires continued follow-up in human intervention trials before a cancer prevention effect of walnuts, per se, should be concluded. Animal research suggests walnuts may be most promising with respect to breast, prostate, colon, and renal cancers, and there is also encouraging epidemiological evidence for a protective effect against pancreatic cancer. In humans, the far-reaching positive effects of a plant-based diet that includes walnuts may include tempering of chronic excess inflammation, with implications for reduced risk of cancer, heart disease, diabetes, metabolic syndrome, and obesity.

Communicating with Impact

Nutrition education is an evolving field in which considerable progress is being made toward improving impact. It is increasingly understood that information is but one component of effective nutrition education. Information must be paired with behavioral approaches, delivered in a manner that is tailored to the group or individual of interest, and communicated through multiple venues or with diverse approaches [33].

Although dietary messages for the public must be largely applicable to the majority, tailoring the message to the audience can be achieved even on a broad scale. Communicators must first seek to understand the individual, as well as social and environmental factors that facilitate or impede change. Relevant characteristics of individuals may include age, gender, health status, financial resources, and a host of factors related directly to food and nutrition, such as knowledge, skills, behaviors, culture, beliefs, attitudes, and perceptions. Individuals live within layers of social networks that are characterized by a milieu of individual characteristics, and environments with varying characteristics of food availability, accessibility, and information.

Behavioral nutrition research increasingly supports the notion that sustainable changes in eating behaviors must not only take into account the levels of influence from individual to societal, but also intervene with consumers on all of these levels [34,35]. For example, nutrition counseling should be personalized, but it is likely helpful to provide the context of population-based dietary guidance for improved understanding.

Taking these layers of influence into account, along with the nutrition evidence, cancer prevention communications can be more effective. Taking walnuts as an example, it is important communicate about single foods appropriately. Because the addition of walnuts to the daily diet may have multiple health benefits, but can likely be realized only within the context of an overall healthful dietary pattern, conveying the role of walnuts in a plant-based diet may have a greater effect than focusing solely on walnuts. For example, consuming walnuts as a snack or as part of a meal can help consumers to meet recommendations to eat less red meat while ensuring adequate protein intake, and ensure adequate n-3 fatty acids in place of saturated and *trans* fats. Nuts are particularly of interest in nutrition given the consumer practice of avoiding them in order to control calories and fat intake. However, nutrition research increasingly supports the importance of healthy fats for good health, and supports a role for walnuts in a calorically appropriate diet. In fact, some nuts are not digested as well as other foods [36,37], which has implications for the caloric value of nuts, and potentially satiety. Therefore, specific information regarding the health benefits of walnuts within the context of energy balance is important for cancer prevention communication.

SUMMARY

Dietary recommendations for reducing cancer risk are largely consistent around the world. A plant-based diet is associated with decreased risk for cancer and other chronic diseases, due in part to reduced chronic inflammation. Nuts and walnuts in particular have been associated with a reduced risk for cancer, as well as CVD, diabetes, obesity, and inflammation markers. The overall dietary and physical activity pattern is critical, however, to reduce chronic disease risk. Strategies for improving dietary behaviors should include both individual and societal/environmental considerations. Walnuts are an example of a food that can be incorporated into nutrition messaging for direct health benefits, as well as in support of meeting broad recommendations for cancer risk reduction.

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