The Role of Diet in Cancer Development and Prevention

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Abstract The World Cancer Research Fund/American Institute for Cancer Research Report on the role of diet in cancer development was published in 2007 and provides the best evidence to date on the subject. This review highlights some recent findings that add to our understanding or raise some questions. The evidence is convincing that body fatness increases cancer risk, including postmenopausal breast cancer; however, recent data indicate that the relationship is heterogeneous by subtype of breast cancer. High plasma vitamin D levels were previously thought to reduce cancer risk, and although recent evidence supports this association for some cancer sites, it also provides evidence of an increased risk of some rarer cancers, including pancreatic and esophageal cancer. Research that adds to our understanding of the association between colorectal cancer risk, fruit and vegetable intake, and also folate and colorectal cancer risk during time periods before and after folic acid fortification is also highlighted.

Keywords Cancer · Prevention · Development · Diet · Physical activity · Vitamin D · Fruit · Vegetable · Breastfeeding · Colorectal cancer · Breast cancer · Body fatness · Folic acid

Introduction

Food, Nutrition and the Prevention of Cancer: A Global Perspective, published by the World Cancer Research Fund

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(WCRF) together with the American Institute for Cancer Research (AICR) [1], is recognized as the most authoritative and influential report on the relationship between food and nutrition and cancer risk. The most recent report, published in 2007, provides eight general (Table 1) and two special nutritional goals and recommendations to protect against cancer from an expert panel. The aim of the present review is to provide an update on findings that add to the evidence provided by the WCRF/AICR in 2007 [1] and to highlight some recent findings that add significantly to our understanding of the relationship between diet and cancer risk.

Body Fatness

The first recommendation made by the WCRF/AICR report is to be as lean as possible within the normal range for body weight (Table 1) [1]. Indeed, the evidence to date is convincing that body fatness increases the risk of esophageal adenocarcinoma and colorectal, pancreatic, endometrial, prostate, and postmenopausal breast cancer [1]. The mechanisms by which body fatness may increase the risk of cancer are well-documented. Concentration of insulin-like growth factor-1 (IGF-1), insulin, and leptin, which are raised in obese individuals, can promote cancer cell growth [2]. Increased insulin and IGF-1 levels, which accompany body fatness, increase the production of sex steroids, including estradiol, androgens, and progesterone, which are also likely to play a role in obesity and cancer risk [3]. There is also evidence to suggest that adult weight gain is positively associated with cancer, particularly postmenopausal breast cancer. Vrieling and colleagues [4•] recently carried out a systematic review and meta-analysis of nine studies published prior to March 2010 that examined the role of weight gain and estrogen receptor (ER)- and/or progesterone receptor (PR)-defined breast cancer. Their results have

Table 1 World Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention

Be as lean as possible within the normal range of body weight:	Ensure that body weight through childhood and adolescent growth projects toward the lower end ($<22.9 \text{ kg/m}^2$) of the normal body mass index at age 21. Maintain body weight within the normal range from age 21. Avoid weight gain and increases in waist circumference throughout adulthood.
Be physically active as part of everyday life:	Be moderately physically active, equivalent to brisk walking, for at least 30 min/d. As fitness improves, aim for ≥ 60 min of moderate, or for ≥ 30 min of vigorous physical activity every day. Limit sedentary habits such as watching television.
Limit consumption of energy-dense foods, avoid sugary drinks, and consume fast foods sparingly, if at all.	
Eat mostly foods of plant origin:	Eat at least 5 portions/servings (at least 400 g, or 14 oz) of a variety of non-starchy vegetables (eg, potatoes) and fruits every day. Eat relatively unprocessed cereals (grains) and/or pulses (peas, beans, lentils) with every meal. Limit refined starchy foods. People who consume starchy roots or tubers as staples should ensure intake of sufficient non-starchy vegetables, fruits, and pulses.
Limit intake of red meat and avoid processed meat:	People who eat red meat should consume $<500 \text{ g}$ (18 oz)/wk; very little, if any, should be processed (eg, sausages, burgers, pepperoni, luncheon meat).
Limit alcoholic drinks:	If alcoholic drinks are consumed, limit consumption to ≤ 2 drinks/d for men and 1 drink/d for women.
Limit consumption of salt; avoid moldy cereals (grains) or pulses:	Avoid salt-preserved, salted, or salty foods. Limit consumption of processed foods with added salt to ensure an intake of $<6 \text{ g}$ (2.4 g sodium)/d.
Limit dietary supplements:	Aim to meet nutritional needs through diet alone.

(Adapted from World Cancer Research Fund/American Institute for Cancer Research [1], <http://www.wcrf.org>, and <http://www.aicr.org>)

shown that adult weight gain and postmenopausal breast cancer risk is heterogeneous according to ER/PR status and is stronger for ER-positive/PR-positive than ER-negative/PR-negative tumors [4•]. Tamimi et al. [5•] further explored this association within the Nurses' Health Study and reported on the relationship between weight gain and breast cancer by breast cancer subtype. At least four major categories of invasive breast cancer have been reproducibly identified by gene expression profiling: luminal subtypes A and B, both of which are hormone receptor positive; *HER2*-type; and basal-like cancers. Tamimi et al. [5•] have shown that the relationship between weight gain and breast cancer may differ by breast cancer subtypes, as weight gain was positively associated with both luminal A and B tumor subtypes, but not with the ER-negative subtypes, and the association with luminal B tumors was significantly stronger than the association with luminal A tumors. The authors did not provide an explanation for this heterogeneity, but their findings are intriguing. Phipps et al. [6•] examined the association among body size, physical activity, and risk of triple-negative breast cancer, which is characterized by a lack of hormone receptor and *HER2* expression and is associated with particularly poor prognosis. Using data from 155,723 women enrolled in the Women's Health Initiative, they did not find differences by breast cancer subtype despite clinical and biological differences, as women in the highest versus lowest body mass index quartile had a 1.35-fold and 1.39-fold increased risk of triple-negative and ER-positive breast cancer, respectively [6•]. Women with the highest amount of recreational physical activity had a similar lower risk of both cancer subtypes as well [6•]. However, a recent editorial by Bernstein and Lacey [7•] highlighted some concerns regarding the potential for misclassification of breast cancer

subtype, in particular *HER2* status, as studies to date have differed in terms of the type of tissue sample (ie, fresh or fixed), reagents, laboratory protocols, and scoring systems used. The authors of the editorial highlighted the need for further collection of samples, especially among large consortia, to identify precise differences between subtypes, in particular less common breast cancer subtypes [7•]. Additional research to determine whether these subtypes are etiologically distinct could stimulate the development of novel targeted approaches to prevention.

Vitamin D and Cancer Risk

The field of vitamin D and cancer research has been moving forward quickly, and there is considerable evidence in the scientific literature citing a protective role for vitamin D against cancer development [8]. The precursor of the physiologically active form of vitamin D is 25-hydroxyvitamin D (25[OH]D), and serum levels of 25(OH)D are dependent on exposure of the skin to sunlight, total vitamin D intake, and other factors (eg, age, skin pigmentation, and obesity) [9, 10]. Several studies have demonstrated that vitamin D may decrease the risk of cancer through various mechanisms, including regulation of cellular proliferation and differentiation, induction of apoptosis, and inhibition of angiogenesis [11, 12]. Consistent inverse associations are evident for vitamin D status and colorectal cancer. Ma et al. [13•] recently provided additional evidence of this inverse association from a meta-analysis of nine studies on vitamin D intake and nine studies on blood 25(OH)D levels and colorectal cancer risk. The pooled relative risks (RRs) of colorectal cancer for the

highest versus lowest categories of vitamin D intake and blood 25(OH)D levels were 0.88 (95% CI, 0.80–0.96) and 0.67 (95% CI, 0.54–0.80), respectively. There was also evidence of a dose–response relationship, as a 10-ng/mL increment in blood 25(OH)D level conferred an RR of 0.74 (95% CI, 0.63–0.89). These results are in agreement with earlier meta-analyses by Gorham et al. [14] and Yin et al. [15], which revealed a 50% lower risk of colorectal cancer associated with a serum 25(OH)D level of greater than 33 ng/mL, compared with less than 12 ng/mL and an OR of 0.57 (95% CI, 0.43–0.76) of colorectal cancer per 20-ng/mL increase of 25(OH)D, respectively. The evidence to support an inverse association between vitamin D and colorectal cancer is therefore expanding.

However, the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers recently published its findings providing the best evidence to date regarding vitamin D and risk of rarer cancers, including endometrial, esophageal, gastric, kidney, non-Hodgkin's lymphoma, ovarian, and pancreatic cancer. This pooling project, a consortium of 10 cohort studies with circulating vitamin D concentrations (25 [OH]D), has shown that higher levels of 25(OH)D concentrations (>100 nmol/L) may not confer any protection against these rarer cancer and may result in an increased risk of some rare cancers. For example, Stolzenberg-Solomon et al. [16] have shown that 25(OH)D concentrations greater than 100 nmol/L were associated with a statistically significant increased risk of pancreatic cancer (RR, 2.12 [95% CI, 1.25–3.64]). In addition, in multivariate-adjusted models, circulating 25(OH)D concentration was not significantly associated with upper gastrointestinal cancer risk [17], endometrial cancer risk [18], or non-Hodgkin's lymphoma [19]. In our own research group, we have shown that esophageal adenocarcinoma risk was significantly greater for individuals with the highest compared with the lowest tertile of vitamin D intake (OR, 1.99 [95% CI, 1.03–3.86; *P* for trend=0.02) in a population-based case-control study [20]. Increased risks of esophageal squamous cell carcinoma [21] and its precursor, squamous dysplasia of the esophagus [22], also have been demonstrated for individuals with the highest serum concentrations of 25(OH)D in a Chinese population. Given these results, recommendations to increase vitamin D concentrations in healthy individuals for prevention of cancer should be carefully considered.

Fruits and Vegetables

The association between fruit and vegetable intake and cancer risk has been investigated by many studies but is controversial because of inconsistent results and weak observed associations. In the 2007 WCRF/AICR report,

the evidence supported a probable lower risk of upper aerodigestive cancers with greater consumption of fruits and vegetables, but this was largely based on the findings of case-control studies [1]. To date, the strongest evidence of a benefit for fruits and vegetables is for renal cell cancer, as a statistically significant inverse association was noted in a recent pooled analysis of prospective studies by Lee et al. [23]; however, the number of cancer cases was not large. Aune et al. [24] recently summarized the evidence in terms of colorectal cancer risk from cohort studies in categorical; linear; and nonlinear, dose–response meta-analyses. Significant inverse associations emerged in nonlinear models for fruits (*P* nonlinearity<0.001) and vegetables (*P* nonlinearity<0.001), and the greatest risk reduction was observed when intake increased from very low levels of intake. Although some caution is needed in interpreting the exact quantities and size of the risk estimates because of the measurement errors associated with use of the dietary assessment methods, the results indicate that there is a low threshold level of between 100 and 200 g/d that can reduce risk by about 10%. Above that level, there seems to be no additional benefit of increasing vegetable intake in terms of colorectal cancer risk, and for fruit, a slight further reduction with higher intakes is observed (~15% reduction for an intake of 600 g/d). This meta-analysis has provided—for the first time—evidence of a nonlinear inverse association between fruit and vegetable intake and colorectal cancer risk, with the greatest reduction in risk at the lower range of intake [24]. As highlighted by the authors, some studies may have missed an effect because the intake in the referent category already may have been sufficient to reduce risk. For example, the mean intake of fruits and vegetables in the reference category was 155 g/d for the European studies included in the meta-analysis, and 200 and 217 g/d for the American and Asian studies, respectively. For fruits and vegetables separately, the figures were 37 and 58 g/d for European studies, 51 and 103 g/d for the American studies, and 48 and 123 g/d for the Asian studies.

Several biologically plausible mechanisms might explain an inverse association between fruit and vegetable intake and colorectal cancer risk. Fruits and vegetables, which are good sources of fiber, increase stool bulk, decrease transit time in the colon, and dilute potential carcinogens [1]. Fruits and vegetables are also good sources of folate, which has been associated with decreased risk of colorectal cancer in several studies [25], but not all studies [1]. In addition, fruits and vegetables are good sources of various antioxidants; vitamins; minerals; and other bioactive compounds, including flavonoids, carotenoids, glucosinolates, indoles, isothiocyanates, and selenium, which may prevent cancer by inducing the activity of detoxifying enzymes and

reducing oxidative stress and inflammation [26]. High intake of fruits and vegetables can also decrease the risk of overweight/obesity [27], an established risk factor for colorectal cancer [1]. The specific mechanism(s) that can explain the threshold effect observed in this study warrant further investigation. Thus, from a public health perspective, targeting individuals and populations with low fruit and vegetable intake might be most effective for colorectal cancer prevention. Nevertheless, public health recommendations for high fruit and vegetable intake are justified because of the greater reductions in risk of coronary heart disease [28], stroke [29], and other cancers [1] associated with higher levels of fruit and vegetable intake.

Folate

Folate plays an essential role in DNA methylation and is necessary for the synthesis of thymine. Folate deficiency can lead to misincorporation of uracil instead of thymine into DNA and increases the number of chromosomal breaks. Previous prospective cohort studies have reported a suggested 20% to 40% reduced risk of colorectal cancer for individuals with the highest folate intake [30••]. The WCRF/AICR report [1] also judged that there was evidence of an inverse association between folate and colorectal cancer risk, and a recent pooled analysis of 13 prospective cohort studies has provided additional evidence to support this [30••]. Kim et al. [30••] studied the relationship between folate intake and colon cancer in 725,134 people, among whom 5,720 incident colon cancers occurred during follow-up. The pooled multivariate RR (95% CI) comparing the highest versus lowest quintile of intake was 0.92 (95% CI, 0.84–1.00) for dietary folate and 0.85 (95% CI, 0.78–0.98) for total folate. However, this risk reduction is modest, and comparing 560 µg/d to 240 µg/d resulted in a 13% reduction (95% CI, 0.78–0.98). In addition, the studies included in this meta-analysis were conducted prior to the mandatory folic acid fortification of grain in the United States and Canada since 1998 that was aimed at preventing neural tube defects. Until recently, the association between folate and colorectal cancer had not been studied in a population since the introduction of folic acid fortification. This is an important consideration, as recent evidence suggests that excessive folate supplementation may actually increase colorectal cancer risk in some individuals. For example, Cole et al. [31] showed that daily folic acid (1 mg) not only did not prevent recurrence of colorectal adenomas compared with placebo, but it appeared to increase the risk of advanced adenomas and multiple adenomas. These results have been attributed to the growth-promoting effects of folic acid on existing undiagnosed precancerous lesions [32]. Therefore, mandatory

folic acid fortification of grain products in the United States may have unintended negative consequences.

Gibson et al. [33] subsequently conducted an analysis using folate intake data from the National Institutes of Health–American Association of Retired Persons Diet and Nutrition Study, a US cohort study of 525,488 individuals 50 to 71 years of age initiated in 1995–1996 to try to address this issue. Dietary, supplemental, and total folate intake were calculated for the pre- and postfortification periods (before and after July 1, 1997) based on a baseline food frequency questionnaire; this included 8.5 years of follow-up after mandatory fortification. The mean energy-adjusted intake of dietary folate before fortification was 297 µg/d, and rose to 391 µg/d after fortification. Overall, folate intake was inversely associated with colorectal cancer risk after fortification, with no evidence of increased risk at the levels of intake reported in the study. Increased total folate intake was linearly associated with decreased risk, and supplemental folic acid was inversely associated as well [33]. Of particular interest was the finding that little or no additional protection was conveyed when total or dietary folate consumption was greater than 500 µg/d [33]. Reassuringly, data from the Cancer Prevention Study II (CPS-II) Nutrition Cohort yielded similar results [34]. From 1999 and 2007, a period entirely after folate fortification, the CPS-II identified 1,023 colorectal cancers and showed that high levels of total folate reduced risk of colorectal cancer, and supported the evidence that there is no indication that dietary fortification or supplementation with folic acid increases colorectal cancer risk [34]. Although these results are reassuring, the authors caution that the 8.5 years of postfortification follow-up may not have been sufficient to observe the relevant effects of folic acid fortification due to the latent period involved in development of invasive colorectal cancer [33]. This research question therefore should be readdressed in these and other cohorts that have measures of folate exposure following the mandatory fortification of grains, and with sufficiently long follow-up to address this issue with greater confidence.

Vitamin B6 (Pyridoxine)

Pyridoxine is one of a group of water-soluble compounds collectively known as vitamin B6. Major food sources of vitamin B6 include meat, fish, poultry, fortified cereals, pulses, starchy vegetables, and some fruits [35]. Together with folate and cobalamin (vitamin B12), vitamin B6 serves as a cofactor for folate-dependent enzymes; is involved in one-carbon metabolism; and is therefore important for DNA synthesis, repair, and methylation [36]. Since the publication of the 2007 WCRF/AICR report [1], additional studies have investi-

gated the role of vitamin B6 in cancer, in particular colorectal cancer risk. Although it is biologically plausible that low vitamin B6 levels may increase colorectal cancer risk through aberrations in DNA synthesis, repair, and methylation [37], findings from prospective studies have been inconsistent. Vitamin B6 may also suppress colorectal carcinogenesis by reducing cell proliferation, angiogenesis, oxidative stress, inflammation, and nitric oxide synthesis [38, 39]. Recently, Larsson et al. [40••] published the results of a systematic review and meta-analysis of evidence to date related to vitamin B6 and blood pyridoxal 5 phosphate (PLP) concentrations, the principal active coenzyme form of B6, and colorectal cancer risk. Nine studies on vitamin B6 intake and four studies on blood PLP levels were included in the meta-analysis. The pooled RRs of colorectal cancer for the highest versus lowest category of vitamin B6 intake and blood PLP levels were 0.90 (95% CI, 0.75–1.07) and 0.52 (95% CI, 0.38–0.71), respectively [40••]. There was heterogeneity among studies of vitamin B6 intake ($P=0.01$), but not among studies of blood PLP levels ($P=0.95$). The authors conducted sensitivity analyses and removed one study that contributed substantially to the heterogeneity among studies of vitamin B6 intake, which then yielded a pooled RR of 0.80 (95% CI, 0.69–0.92) [40••]. A dose–response relationship was also identified, and the risk of colorectal cancer decreased by 49% for every 100-pmol/mL increase (~2 SDs) in blood PLP levels (RR, 0.51 [95% CI, 0.38–0.69]) [40••]. This meta-analysis is the best evidence to date of an inverse association between vitamin B6 intake and blood PLP levels and colorectal cancer risk. Although vitamin B6 is found in a wide variety of foods, many older people do not have adequate intake of this nutrient, and it is estimated that in the United States, the prevalence of inadequate vitamin B6 intake for adults older than 50 years of age is about 20% for men and 40% for women [41]. An inverse association between plasma PLP levels also has been shown for risk of colorectal adenomas. For example, the AFPPS (Aspirin Folate Polyp Prevention Study), a randomized trial of folic acid supplementation, showed that the incidence of new colorectal adenomas in individuals with a history of adenomas was 22% lower in those in the highest quartile of baseline plasma PLP level (RR, 0.78 [95% CI, 0.61–1.00]) [42]. Similarly, in the Nurses' Health Study, women in the highest quartile of plasma PLP had a non-statistically significant lower risk of distal colorectal adenoma than did women in the lowest quartile after adjustment for potential confounders (RR, 0.69 [95% CI, 0.41–1.15]) [43]. The association between vitamin B6 intake and colorectal cancer risk now warrants further investigation in a large, randomized clinical trial.

Breastfeeding

The WCRF/AICR [1] made a special recommendation in 2007 that mothers should breastfeed. Additional evidence in support of this recommendation has shown that breastfeeding for 4 or more months is associated with a 40% reduction (95% CI, 0.40–0.90) in basal-like breast cancer tumors compared with those who had never breastfed [5•]. Results from the CBCS (Carolina Breast Cancer Study), a case-control study that included a total of 1,424 breast cancer cases from Caucasian and African American women, also showed an inverse association between lactation and basal-like tumors, and women who breastfed for 4 or more months had a 30% reduced risk compared with those who had never breastfed [44]. This is an especially important finding, as the identification of risk factors for these less common subtypes, which also have a poorer prognosis, has important implications for prevention of this tumor subtype.

Conclusions

The present review highlights recent findings that increase our understanding of the relationship between diet and cancer. The findings by Tamimi et al. [5•], which demonstrate a heterogeneous relationship between both weight gain and breastfeeding and breast cancer risk by subtype of breast cancer, are intriguing and warrant further investigation. This will require the collection of samples, especially among large consortia, to identify precise differences in the role of weight gain and other important lifestyle factors (including waist circumference, percent fat, diet, physical activity, and smoking) by breast cancer subtype, in particular the relationship between lifestyle factors and the less common breast cancer subtypes (eg, triple-negative breast cancer). Additional research to determine whether these subtypes are etiologically distinct could stimulate the development of novel targeted approaches to prevention.

The findings by Stolzenberg-Solomon et al. [16] and Abnet et al. [17], which demonstrate a positive association between 25(OH)D and pancreatic cancer and esophageal cancer, respectively, highlight the need for careful consideration of the evidence before any recommendations for vitamin D supplementation are made. Additional research in countries in which vitamin D intake and status is low due to a lack of vitamin D food fortification and low UV exposure may provide additional evidence that will help clarify the role of vitamin D and cancer risk.

The updated evidence highlighted in this review is largely from meta-analyses, and there are, of course, limitations of meta-analyses of dietary data. Adjustment

for potential confounders is limited by adjustment within individual studies included, and inadequate control for confounders may bias the results toward exaggeration or underestimation of risk estimates. Although most studies do adjust for other known risk factors for cancer and for the specific cancer of interest, residual or unknown confounding cannot be excluded. It is also likely that intake of nutrients associated with a healthy diet is also associated with healthy behaviors that may be protective against cancer, such as greater physical activity, less smoking, lower alcohol consumption, and higher folate intake.

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