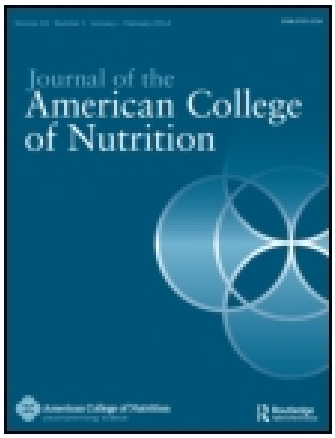

Journal of the American College of Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uacn20

Applying the Precautionary Principle to Nutrition and Cancer

Joseph F. Gonzales R.D.[a], Neal D. Barnard M.D.[a], David J.A. Jenkins M.D., Ph.D.[b], Amy J. Lanou Ph.D.[c], Brenda Davis R.D.[d], Gordon Saxe M.D., Ph.D.[e] & Susan Levin M.S., R.D.[a]

[a] Physicians Committee for Responsible Medicine, Clinical Research, Washington, D.C.

[b] Department of Medicine and Nutritional Sciences, University of Toronto, Toronto, CANADA

[c] Department of Health and Wellness, University of North Carolina, Asheville, North Carolina

[d] Personal Consultant, Kelowna, CANADA

[e] University of California, San Diego, California

Published online: 28 May 2014.

To cite this article: Joseph F. Gonzales R.D., Neal D. Barnard M.D., David J.A. Jenkins M.D., Ph.D., Amy J. Lanou Ph.D., Brenda Davis R.D., Gordon Saxe M.D., Ph.D. & Susan Levin M.S., R.D. (2014) Applying the Precautionary Principle to Nutrition and Cancer, Journal of the American College of Nutrition, 33:3, 239-246, DOI: 10.1080/07315724.2013.866527

To link to this article: http://dx.doi.org/10.1080/07315724.2013.866527

Review

Applying the Precautionary Principle to Nutrition and Cancer

Joseph F. Gonzales, R.D., Neal D. Barnard, M.D., David J.A. Jenkins, M.D., Ph.D., Amy J. Lanou, Ph.D., Brenda Davis, R.D., Gordon Saxe, M.D., Ph.D., Susan Levin, M.S., R.D.

Physicians Committee for Responsible Medicine, Clinical Research, Washington, D.C. (J.F.G., N.D.B., S.L.); Department of Medicine and Nutritional Sciences, University of Toronto, Toronto, CANADA (D.J.A.J.); Department of Health and Wellness, University of North Carolina, Asheville, North Carolina (A.J.L.); Personal Consultant, Kelowna, CANADA (B.D.); University of California, San Diego, California (G.S.)

Key words: cancer, risk, diet, meat, milk, dairy, soy, alcohol

Primary Objective: Research has identified certain foods and dietary patterns that are associated with reduced cancer risk and improved survival after cancer diagnosis. This research has formed the basis for dietary guidance issued by cancer organizations. Unfortunately, gaps within nutrition research have made it difficult to make recommendations in some areas. This review specifies suggested dietary guidance in which evidence of a dietary influence on cancer risk is substantial, even if not conclusive. Evidence summaries within the review are based on the 2007 report of the World Cancer Research Fund/American Institute for Cancer Research. This review also describes advantages and disadvantages of following the suggested dietary guidance and includes putative mechanisms involved in cancer progression.

Main Outcomes and Results: Suggested dietary guidance where evidence is sufficiently compelling include (1) limiting or avoiding dairy products to reduce the risk of prostate cancer; (2) limiting or avoiding alcohol to reduce the risk of cancers of the mouth, pharynx, larynx, esophagus, colon, rectum, and breast; (3) avoiding red and processed meat to reduce the risk of cancers of the colon and rectum; (4) avoiding grilled, fried, and broiled meats to reduce the risk of cancers of the colon, rectum, breast, prostate, kidney, and pancreas; (5) consumption of soy products during adolescence to reduce the risk of breast cancer in adulthood and to reduce the risk of recurrence and mortality for women previously treated for breast cancer; and (6) emphasizing fruits and vegetables to reduce risk of several common forms of cancer.

Conclusion: By adopting the precautionary principle for nutrition research, this review aims to serve as a useful tool for practitioners and patients.

INTRODUCTION

Scientific studies have clarified many aspects of how foods affect cancer risk, prompting leading organizations to issue recommendations for cancer prevention [1]. There are, however, a number of areas in nutritional science in which scientific evidence has been insufficient for authorities to issue guidance with confidence. However, individuals making dietary decisions from day to day cannot wait for the evolution of scientific consensus. To protect themselves and their families, they have to act on the best available evidence.

The concept of the precautionary principle is commonly understood in toxicology and environmental health. For example, the European Union invokes the precautionary principle "when there are reasonable grounds for concern that potential hazards may affect the environment or human, animal or plant health, and when at the same time the available data preclude a detailed risk evaluation" [2, p. 9].

This approach is not as familiar in nutritional sciences but may play a useful role in cases in cancer prevention, due to the limited practicality of randomized controlled trials in certain areas and the long latency period from exposure to cancer diagnoses [3].

We have therefore developed a set of dietary principles to be used in 6 areas in which evidence of a dietary influence on cancer risk is substantial, even if not conclusive.

In the sections below, evidence summaries are based on the 2007 report of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global*

Address correspondence to: Joseph Gonzales, RD, Physicians Committee for Responsible Medicine, Clinical Research, 5100 Wisconsin Ave NW, Washington, DC 20016. E-mail: josephfrankgonzales@gmail.com

Journal of the American College of Nutrition, Vol. 33, No. 3, 239–246 (2014)
Published by Taylor & Francis Group, LLC

Perspective, and on additional evidence sources not mentioned by WCRF/AICR [6]. These evidence sources were either published after the WCRF/AICR 2007 publication or contain information regarding potential advantages and disadvantages of suggested dietary guidance aside from their potential effect on cancer risk. For each topic we used available meta-analyses on cohort studies provided by the WCRF/AICR and listed the number of studies reviewed by their 2007 report.

Overall, evidence suggests that diets emphasizing foods from plant sources—vegetables, fruits, whole grains, and legumes—are associated with lower cancer risk, as well as reduced risk for cardiovascular disease, diabetes, and hypertension [4]. Plant-based diets tend to promote a healthy body weight [5], which, in turn, is associated with reduced risk of certain common forms of cancer [6].

These suggested dietary recommendations are not a comprehensive dietary plan. Rather, they relate to specific areas where evidence is sufficiently compelling to merit dietary changes.

MILK AND DAIRY PRODUCTS

Suggested Dietary Guidance

Limiting or avoiding dairy products may reduce the risk of prostate cancer.

Evidence Summary

The WCRF/AICR findings linking milk and dairy product consumption to prostate cancer risk were based on 10 cohort studies, 13 case-control studies, and 2 ecological studies. A meta-analysis was possible on 8 cohort studies, giving a summary effect estimate of 1.06 (95% confidence interval [CI], 1.01–1.11) per serving/day with moderate heterogeneity. Although the evidence is inconsistent, the WCRF/AICR concludes that diets high in calcium are a probable cause of prostate cancer and that limited data suggest that milk and dairy products cause prostate cancer through actions of high calcium intake and/or increased levels of insulin-like growth factor-I (IGF-I) [6].

In the Health Professionals Follow-Up Study, relative risk (RR) was 60% higher for men consuming 2 milk servings per day compared to zero servings per day (RR = 1.60, 95% CI, 1.2–2.1) [7]. A meta-analysis of 11 case-control studies found that the combined odds ratio (OR) for the highest consumption of milk products was 1.68 (OR = 1.68, 95% CI, 1.34–2.12) [8].

The European Prospective Investigation into Cancer and Nutrition [EPIC] study, involving 142,251 men, showed a 22% increased risk of prostate cancer for men consuming a mean of 27 g of dairy protein per day, compared to those consuming a mean of 10 g per day (hazard ratio 1.22, 95% CI, 1.07–1.41). One glass of skim milk contains 8.4 g of protein. The researchers estimated that every 35 g of dairy protein consumed daily can increase prostate cancer risk by 32% (hazard ratio 1.32, 95% CI, 1.01–1.72) [9]. Calcium from dairy products was also positively associated with risk, supporting the hypothesis that high intake of protein or calcium from dairy products may increase prostate cancer risk.

Putative mechanisms by which milk contributes to increased prostate cancer risk include the ability of a large oral calcium dose to suppress vitamin D activation [7, 10] and the tendency of milk to increase serum IGF-I concentrations [11, 12].

The possibility that dietary calcium plays a role in prostate cancer risk is supported by the observation that calcium supplements apparently increase risk, just as milk does [10]. The Heath Professionals Follow-Up Study found a 51% increased risk for fatal prostate cancer among men supplementing $\geq$401 mg of calcium per day compared to those who used no calcium supplements (RR = 1.51, 95% CI, 1.09–2.10) [10].

Vitamin D has been shown in some [13] but not all studies [14] to play a protective role in relation to prostate cancer. Produced through the action of sunlight on the skin (or ingested), vitamin D requires activation in the liver and kidneys. A high oral calcium load suppresses this activation process. In addition, high intake of phosphate from dairy products can decrease vitamin D activation [15].

Milk ingestion also increases the concentration of IGF-I in the bloodstream [16]. In men and women aged 55 to 85 years the ingestion of 3 8-oz. servings of milk daily for 12 weeks has been shown to increase serum IGF-I concentration by approximately 10% [17]. An analysis from the EPIC study, involving 4731 participants, showed that ingested dairy protein increased serum IGF-I concentrations, whereas non-dairy calcium and protein sources had no significant effect on IGF-I concentrations [11].

Advantages

Limiting saturated fat and cholesterol intake from dairy products may decrease cardiovascular disease risk [18]. Most people (approximately 70% of the world's population) are hypolactasic after weaning and therefore have difficulty digesting lactose [19]. For affected individuals, especially those with other gastrointestinal disorders, avoiding milk products may reduce the symptoms associated with digestive problems.

Disadvantages

Limiting or avoiding milk and dairy products may reduce calcium intake if individuals rely on milk and dairy products as a primary calcium source. This is relevant not only for bone integrity but also for prevention of colorectal cancer, a malignancy shown to be reduced in individuals consuming more calcium [20]. High levels of calcium (or milk) consumption have not been shown to significantly improve bone health [21]. However, dietary calcium is essential and can be obtained through green leafy vegetables, legumes, and calcium-fortified foods, such as non-dairy milks.

ALCOHOL

Suggested Dietary Guidance

Limiting or avoiding alcohol may reduce the risk of cancers of the mouth, pharynx, larynx, esophagus, colon and rectum, and breast.

Evidence Summary

The WCRF/AICR investigated the role of alcohol in cancer risk. For cancers of the mouth, pharynx, and larynx, findings were based on 5 cohort studies on total alcoholic drinks, 89 case-control studies, and 4 ecological studies. A quantification of the degree of risk came from a meta-analysis of 2 cohort studies, showing a consistent and dose-related effect, with one drink consumed per week increasing risk by 24% (OR = 1.24, 95% CI, 1.18–1.30) [22]. The EPIC study produced similar findings that were consistent and dose related. Every 10 g of alcohol consumed per day increased risk of squamous cell carcinoma of the upper aero-digestive tract by approximately 10–15%, respectively (RR = 1.10, 95% CI, 1.08–1.13; RR = 1.15, 95% CI, 1.12–1.18) [23]. One standard drink holds 13.7 g of alcohol. Women were at higher risk than men.

For esophageal cancer, findings from the WCRF/AICR report were based on 8 cohort studies on total alcoholic drinks, 56 case-control studies, and 10 ecological studies [6]. Six of the 8 cohort studies found an increased risk for those drinking the most alcohol compared to the least; however, only 4 of the studies found statistically significant relationships. A meta-analysis was possible on 20 case-control studies, showing that 1 drink per week increased risk by approximately 4% (OR = 1.04, 95% CI, 1.03–1.05) [24].

For colorectal cancer, findings were based on 24 cohort studies investigating total alcoholic drinks, 13 cohort studies, and 41 case-control studies specifically investigating ethanol intake. Although a meta-analysis on total alcoholic drinks failed to show an increased colorectal risk, a meta-analysis on alcohol (as ethanol) found a consistent and dose-related relationship, with 10 g of ethanol consumed on a daily basis increasing risk by approximately 9% (OR = 1.09, 95% CI, 1.03–1.14) [25].

A recent review of 27 cohort and 34 case-control studies by the International Agency for Research on Cancer showed that moderate drinkers (2–3 drinks per day) had a 21% increased risk of colorectal cancer risk compared to nondrinkers or occasional alcohol drinkers (RR = 1.21, 95% CI, 1.13–1.28). Risk was higher still for heavier drinkers. This meta-analysis concludes that consumption of more than 1 alcoholic drink per day has a strong relationship with increased colorectal cancer risk [26].

For breast cancer, findings were based on 11 cohort studies, 31 case-control studies, and 2 ecological studies investigating total alcoholic drinks and breast cancer at all ages, among other analyses. Additionally, studies reviewed on alcohol intake (as ethanol) and breast cancer risk include 25 cohort studies, 29 case-control studies, and 4 ecological studies. The findings were generally consistent and dose related. A meta-analysis of 9 cohort studies showed a 10% increased risk per 10 g of ethanol consumed on a daily basis percent (OR = 1.10, 95% CI, 1.06–1.14) [27]. Later studies support these findings. For example, the Million Women Study showed that every additional 10 g of alcohol consumed per day increased risk by 12% (RR = 1.12, 95% CI, 1.09–1.14) [28].

Most evidence suggests that the type of alcoholic beverage is not an important factor in cancer risk; the casual factor is evidently ethanol itself. However, the degree of risk varies, depending on cancer type. One drink per day increases breast cancer risk but the same amount has a weaker association with cancers arising in other sites. Men appear to be at greater risk than women.

Putative mechanisms by which alcohol contributes to cancer risk include reactive metabolites of alcohol, such as acetaldehyde, lipid peroxidation, and generation of free-radical oxygen species [29, 30]. Alcohol may also disrupt folate metabolism [31].

Advantages

Avoiding alcohol prevents the problems associated with more than moderate use. These problems include cirrhosis of the liver and hepatocellular carcinoma [32], pancreatitis [33], pregnancy complications [34], obesity [35], accidents [36], and suicide [36].

Disadvantages

Moderate alcohol use (up to 1 drink for women and 2 drinks for men per day) is associated with reduced risk of cardiovascular events and Alzheimer's disease [37, 38]. The effect of alcohol abstinence on these conditions is uncertain [39].

RED AND PROCESSED MEAT

Suggested Dietary Guidance

Avoiding red and processed meat may reduce the risk of cancers of the colon and rectum.

Evidence Summary

For the relationship between colorectal cancer and red meat intake, the WCRF/AICR report based its findings on 16 cohort studies and 71 case-control studies [6]. In a meta-analysis of prospective studies, findings were consistent and dose related, with every 120 g of red meat consumed on a daily basis increasing risk by an estimated 28% (RR = 1.28, 95% CI, 1.18–1.39) [40]. For processed meat, findings were based on 14 cohort studies and 44 case-control studies. From a meta-analysis of 5 cohort studies, the findings were consistent and dose related,

with every 50 g consumed on a daily basis increasing risk by 21% (RR = 1.21, 95% CI, 1.04–1.42) [41]. In May of 2011, the WCRF/AICR's Continuous Update Project held that red and processed meats are convincingly associated with an increased colorectal cancer risk [42].

Putative mechanisms by which red and processed meat contribute to cancer risk include the abundance of heme iron [43], nitrites [44], heterocyclic amine formation [45], and the overabundance of essential amino acids and other nutrients that promote cell growth [46].

Advantages

Aside from effects on colorectal cancer risk, avoiding red and processed meat may reduce the risk of diabetes [47], hypertension [48], and stroke and cardiovascular disease [49, 50].

Disadvantages

Red meat is a concentrated source of protein, iron, and zinc. However, adequate intakes of these nutrients can easily be obtained in varied plant-based diets.

MEATS COOKED AT HIGH TEMPERATURE

Suggested Dietary Guidance

Avoiding grilled, fried, and broiled meats may reduce the risk of cancers of the colon, rectum, breast, prostate, kidney, and pancreas. In this context, *meat* refers to red meat, poultry, and fish.

Evidence Summary

The National Toxicology Program lists 4 heterocyclic amines (HCAs) as reasonably anticipated to be a human carcinogen in the 11th Report on Carcinogens from the US Department of Health and Human Services [51]. The 4 identifiable HCAs are 2-amino-3-methylimidazo[4,5-*f*]quinoline,2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline, 2-amino-3,8-dimethylimazo[4,5-*f*] quinoxaline, and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine. These compounds are associated with cancer of the colon and rectum, with weaker associations with cancers of the breast, prostate, kidney, and pancreas [51].

HCAs are genotoxic, mutagenic compounds, which form from creatine and amino acids in cooked skeletal muscle, increasing in concentration with longer cooking times and higher temperatures [52]. When ingested, HCAs can disrupt DNA synthesis. Some meats may also contain polycyclic aromatic hydrocarbons, which form when organic substances are burned incompletely. For example, when grilling meat over a direct flame, droplets of fat come in contact with the flame, causing a reaction where PAHs stick to the surface of the cooked product. Similar to HCAs, concentration of PAHs increase as the temperature rises [53].

Advantages

Avoiding grilled, broiled, and fried meats can reduce saturated fat and cholesterol intake, reducing the risk of cardiovascular disease [4].

Disadvantages

There are no disadvantages to avoiding meats cooked at high temperatures.

SOY PRODUCTS

Suggested Dietary Guidance

Consumption of soy products during adolescence may reduce the risk of breast cancer arising in adulthood. Soy products may also reduce the risk of recurrence and mortality for women previously treated for breast cancer.

Evidence Summary

Recent studies have examined the effects of soy products on breast cancer risk. Chinese women who consumed more than 11.3 g of soy protein on a daily basis during adolescence, compared to less than 2.7 g, had a 43% reduced risk of developing premenopausal breast cancer (RR = 0.57, 95% CI, 0.34–0.97) [54]. The equivalent of 1 cup of fortified soymilk, a $^1/_2$ cup of tofu, or a $^1/_2$ cup of cooked soybeans is approximately 10 g of soy protein. The same study found a significant association for women who consumed more than 12.8 g of soy protein on a daily basis throughout adulthood, compared to 4.9 g or less, showing a 59% reduced risk of developing premenopausal breast cancer (RR = 0.41, 95% CI, 0.25–0.70). In a case-control study, findings were consistent and dose related, with >122.2 g of total soy consumed per day (compared to <45.7 g per day) reducing premenopausal and postmenopausal breast cancer risk by 64% (OR = 0.36, 95% CI, 0.20–0.64). The risk reduction was 92% for developing estrogen- and progesterone receptor–positive tumors in postmenopausal Korean women (OR = 0.08, 95% CI, 0.03–0.22) [55]. One-half cup of tofu weighs approximately 125 g [56].

An earlier study investigating the role of tofu on breast cancer risk in Asian Americans showed that each additional serving of tofu consumed per week reduced the risk of premenopausal or postmenopausal breast cancer by 15% (OR = 0.85, 95% CI, 0.74–0.99) [57].

A large prospective study of the effect of soy products on breast cancer recurrence and survival showed that 11 g

of soy protein consumed on a daily basis reduced mortality and recurrence by approximately 30% in both pre- and postmenopausal Chinese women with either estrogen-positive or estrogen-negative cancer (hazard ratio = 0.71, 95% CI, 0.54–0.92 for total mortality and hazard ratio = 0.68, 95% CI, 0.54–0.87 for recurrence) [58].

In Western populations observation of 3088 breast cancer survivors of the Women and Healthy Eating and Living study showed that as isoflavone intake increased the risk of overall mortality decreased [59]. Another Western cohort (Life After Cancer Epidemiology) observing 1954 postmenopausal women with breast cancer showed a reduced risk of cancer recurrence with increasing amounts of the isoflavones daidzein and glycetin, compared to those who did not consume isoflavones. There was an approximate 60% reduction in recurrence for women treated with tamoxifen in the highest category of daidzein intake (>1453 μg/day) compared to the lowest (<7.7 μg/day; hazard ratio = 0.48, 95% CI, 0.21–0.79) [60].

Putative mechanisms by which soy products contribute to decreased cancer risk include the ability of genistein to increase apoptosis and to reduce cell proliferation and blood vessel growth and to modulate sex hormone effects and to the antioxidant content of legumes [61, 62].

Advantages

Soy products often serve as replacements for meat and dairy products and may therefore reduce the risk of coronary heart disease [63, 64].

Soy products have also been linked to improved bone health and reduced fracture risk in women [65].

Disadvantages

When used in large amounts, soy protein concentrates and isolates have been shown to increase insulin-like growth factor I [66–68], an effect also seen with dairy products [18], suggesting that traditional soy foods should be favored over soy protein concentrates and isolates (e.g., pills and powders).

FRUITS AND VEGETABLES

Suggested Dietary Guidance

Emphasizing fruits and vegetables in your diet will likely reduce the risk of several common forms of cancer.

Evidence Summary

Fruits and vegetables contain fiber and phytochemicals (including antioxidants) that have been shown to reduce cancer risk. According to the WCRF/AICR, several types of vegetables and fruits can reduce the risk of cancer at multiple sites, although with weak associations [69].

The EPIC study followed 25,623 men and women in the Greek cohort for a median of 7.9 years, finding statistically significant inverse relationships with cancer risk overall (hazard ratio per quintile = 0.94, 95% CI, 0.88–0.99) [70]. The lowest to highest quintiles for fruit and vegetable consumption in women were 567–1314 g/day and 522–1371 g/day for men.

A large meta-analysis of 32 observational studies and 10,057 cases of esophageal squamous cell carcinoma found that higher intake of vegetables was associated with a 64% decreased risk of developing esophageal cancer (summary RR = 0.56, 95% CI, 0.45–0.69), whereas higher intake of fruits led to a 67% decreased risk (summary RR = 0.53, 95% CI, 0.44–0.64) [71] compared to low intake.

Often fruits and vegetables are studied by their genus in the plant kingdom (i.e., cruciferous/Brassicaceae vegetables, such as broccoli and cabbage, or allium vegetables, such as garlic and onions) or by individual constituents such as beta-carotene, folate, and certain vitamins.

A meta-analysis of 35 studies found that higher intakes of cruciferous vegetables are associated with an 18% reduction in the risk of colorectal cancer (RR = 0.82, 95% CI, 0.75–0.90) [72]. Other research suggests that cruciferous vegetables can reduce the risk many cancers, some including cancer of the lung [73] and stomach [74]. A pooled analysis of 8 cohort studies including many US-based cohorts observed how carotenoid content may lower breast cancer risk. Women consuming more total carotenoids lowered their risk of breast cancer by 19% (RR = 0.81, 95% CI, 0.68–0.96) compared to women who consumed lower amounts [75]. For fruit and vegetable intake and breast cancer risk, a meta-analysis on 15 prospective studies found that a higher intake of fruits and vegetables combined led to a 11% decreased breast cancer risk (RR = 0.89, 95% CI, 0.80–0.99) [76].

For gastric cancer, those eating large amounts of tomato products reduced their risk of gastric cancer by 27% (OR = 0.73, 95% CI, 0.60–0.90) compared to those who ate the least, according to a meta-analysis of 21 cohort and case-control studies [77]. Controlling for specific nutrients presents a challenge in nutritional research due to the synergistic role of the abundant nutrients in fruits and vegetables. Therefore, observing dietary patterns is often important. A review on dietary patterns and gastric cancer found that participants whose diets reflect high amounts of meat and fat (i.e., Western diet with low amounts of fruits and vegetables) showed a 2-fold increased risk compared to those who ate a healthy/prudent diet full of fruits and vegetable [78]. Garlic and other allium vegetables also have a significant effect on reducing gastric cancer risk [79].

Several putative mechanisms have been suggested for the reduction in cancer risk associated with fruit and vegetable intake. Antioxidants limit reactive oxygen species. Some components of vegetables may have antitumor properties, such as glycosylates

(a precursor to isothiocyanates) and indole-3-carbonol (precursor to 3,3′-diindolylmethane), which have been shown to induce phase II enzymes responsible for eliminating reactive oxygen species and repairing DNA systems [80, 81]. Some components in soybeans, green tea, turmeric, grapes, tomatoes, and other plant foods have the ability to regulate apoptosis, an important pathway for cancer prevention [82].

Advantages

Fruits and vegetables have health effects beyond cancer prevention. A total of 71,910 female participants in the Nurses' Health Study and 37,725 male participants in the Health Professionals Follow-Up Study who were free of major chronic disease completed baseline semiquantitative food-frequency questionairres in 1984 and 1986, respectively. Total fruit and vegetable intake was inversely associated with risk of cardiovascular disease but not with overall cancer incidence, with relative risk for an increment of five servings daily of 0.88 (95% CI = 0.81 to 0.95) for cardiovascular disease [83]. Green leafy vegetables had the greatest effect. Furthermore, a meta-analysis of 12 cohort studies found that eating more than 5 servings of fruits and vegetables daily reduces the risk of coronary heart disease by 17% (RR = 0.83, 95% CI, 0.77–0.89) compared to less than 3 servings per day [84]. This study included 278,459 individuals with a median follow-up of 11 years. In general, fruits and vegetables have been linked to reduced risk of stroke [85], hypertension [86], and type 2 diabetes [87, 88].

Disadvantages

There are no disadvantages for healthy people eating more fruits and vegetables.

REFERENCES

1. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T: 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 62:30–67, 2012.
2. Commission of the European Communities: "*Communication from the Commission on the Precautionary Principle*." Brussels, Belgium: Commission of the European Communities, 2000. Accessed at: http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52000DC0001.
3. Blumberg J, Heaney RP, Huncharek M, et al.: Evidence-based criteria in the nutritional context. Nutr Rev 68:478–484, 2010.
4. Craig WJ, Mangels AR: Position of the American Dietetic Association: vegetarian diets. J Am Diet Assoc 109:1266–1282, 2009.
5. Tonstad S, Butler T, Yan R, Fraser GE: Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care 32: 791–796, 2009.
6. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
7. Giovannucci E, Rimm EB, Wolk A, et al.: Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 58:442–447, 1998.
8. Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A: Milk consumption is a risk factor for prostate cancer: meta-analysis of case-control studies. Nutr Cancer 48:22–27, 2004.
9. Allen NE, Key TJ, Appleby PN, et al.: Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 98:1574–1581, 2008.
10. Giovannucci E, Liu Y, Stampfer MJ, Willett WC: A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev 15:203–210, 2006.
11. Crowe FL, Key TJ, Allen NE, et al.: The association between diet and serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 18:1333–1340, 2009.
12. Holmes MD, Pollak MN, Willett WC, Hankinson SE: Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 11:852–861, 2002.
13. Holick MF: Vitamin D: its role in cancer prevention and treatment. Prog Biophys Mol Biol 92:49–59, 2006.
14. Albanes D, Mondul AM, Yu K, et al.: Serum 25-hydroxyvitamin D and prostate cancer risk in a large nested case-control study. Cancer Epidemiol Biomarkers Prev 20:1850–1860, 2011.
15. Newmark HL, Heaney RP: Dairy products and prostate cancer risk. Nutr Cancer 62:297–299, 2010.
16. Qin LQ, He K, Xu JY: Milk consumption and circulating insulin-like growth factor-I level: a systematic literature review. Int J Food Sci Nutr 60(suppl 7):330–340, 2009.
17. Heaney RP, McCarron DA, Dawson-Hughes B, et al.: Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 99:1228–1233, 1999.
18. Bemelmans WJ, Lefrandt JD, Feskens EJ, et al.: Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1. Atherosclerosis 163:113–120, 2002.
19. Lomer MC, Parkes GC, Sanderson JD: Review article: lactose intolerance in clinical practice—myths and realities. Aliment Pharmacol Ther 27:93–103, 2008.
20. Cho E, Smith-Warner SA, Spiegelman D, et al.: Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 96:1015–1022, 2004.
21. Feskanich D, Willett WC, Colditz GA: Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr 77:504–511, 2003.
22. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
23. Weikert C, Dietrich T, Boeing H, et al.: Lifetime and baseline alcohol intake and risk of cancer of the upper aero-digestive tract in

the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Cancer 125:406–412, 2009.
24. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
25. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
26. Fedirko V, Tramacere I, Bagnardi V, et al.: Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies. Ann Oncol 22:1958–1972, 2011.
27. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
28. Allen NE, Beral V, Casabonne D, et al.: Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 101:296–291, 2009.
29. Mahabir S, Baer DJ, Johnson LL, Dorgan JF, Campbell W, Brown E, et al.: The effects of moderate alcohol supplementation on estrone sulfate and DHEAS in postmenopausal women in a controlled feeding study. Nutr J 3:1–4, 2004.
30. Wiseman MJ: The World Cancer Research Fund Expert Report: the next steps. IARC Sci Publ 156:523–524, 2002.
31. Poschl G, Stickel F, Wang XD, Seitz HK: Alcohol and cancer: genetic and nutritional aspects. Proc Nutr Soc 63:65–71, 2004.
32. Tornai I: Role of environmental factors in the etiology of hepatocellular carcinoma. Orv Hetil 151:1132–1136, 2010.
33. Jha RK, Ma Q, Sha H, Palikhe M: Acute pancreatitis: a literature review. Med Sci Monit 15:RA147–RA156, 2009.
34. Ismail S, Buckley S, Budacki R, Jabbar A, Gallicano GI: Screening, diagnosing and prevention of fetal alcohol syndrome: is this syndrome treatable? Dev Neurosci 32:91–100, 2010.
35. Wannamethee SG, Shaper AG: Alcohol, body weight, and weight gain in middle-aged men. Am J Clin Nutr 77:1312–1317, 2003.
36. Talarowska M, Ostrycharczyk K, Florkowski A, Jurczyk AP, Gałecki P: The risk of death following the consumption of ethanol based on forensic research material. Pol Merkur Lekarski 29: 100–102, 2010.
37. Vogel RA: Alcohol, heart disease, and mortality: a review. Rev Cardiovasc Med 3:7–13, 2002.
38. Weyerer S, Schäufele M, Wiese B, et al.: Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 years and older. Age Ageing 40:456–463, 2011.
39. Britton A, Marmot MG, Shipley M: Who benefits most from the cardioprotective properties of alcohol consumption—health freaks or couch potatoes? J Epidemiol Community Health 62:905–908, 2008.
40. Larsson SC, Wolk A: Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer 119: 2657–2564, 2006.
41. World Cancer Research Fund and the American Institute for Cancer Research. "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
42. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Report Summary. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011*. Washington, DC: American Institute for Cancer Research, 2011. Accessed at: http://www.wcrf.org/PDFs/Colorectal-cancer-report-summary-2011.pdf
43. Bastide NM, Pierre FH, Corpet DE: Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila) 4:177–184, 2011.
44. Loh YH, Jakszyn P, Luben RN, Mulligan AA, Mitrou PN, Khaw KT: N-nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study. Am J Clin Nutr 93:1053–1061, 2011.
45. Sinha R, Kulldorff M, Chow WH, Denobile J, Rothman N: Dietary intake of heterocyclic amines, meat-derived mutagenic activity, and risk of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 10:559–562, 2001.
46. Gulati P, Gaspers LD, Dann SG, et al.: Amino acids activate mTOR complex 1 via Ca2 + /CaM signaling to hVps34. Cell Metab 7: 456–465, 2008.
47. Aune D, Ursin G, Veierød MB: Meat consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. Diabetologia 52:2277–2287, 2009.
48. Berkow SE, Barnard ND: Blood pressure regulation and vegetarian diets. Nutr Rev 63:1–8, 2005.
49. Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A: Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med 169:562–571, 2009.
50. Babio N, Sorlí M, Bulló M, et al.: Association between red meat consumption and metabolic syndrome in a Mediterranean population at high cardiovascular risk: cross-sectional and 1-year follow-up assessment. Nutr Metab Cardiovasc Dis 22:200–207, 2012.
51. US Department of Health and Human Services, Public Health Service: National Toxicology Program. 2005. 11th Report on Carcinogens. Accessed at: http://ntp.niehs.nih.gov/ntp/roc/toc11.html
52. Pais P, Salmon CP, Knize MG, Felton JS: Formation of mutagenic/carcinogenic heterocyclic amines in dry-heated model systems, meats, and meat drippings. J Agric Food Chem 47:1098–1108, 1999.
53. World Cancer Research Fund and the American Institute for Cancer Research: "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
54. Lee SA, Shu XO, Li H, et al.: Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am J Clin Nutr 89:1920–1926, 2009.
55. Cho YA, Kim J, Park KS, et al.: Effect of dietary soy intake on breast cancer risk according to menopause and hormone receptor status. Eur J Clin Nutr 64:924–932, 2010.
56. US Department of Agriculture: National Nutrient Database for Standard Reference. Tofu, raw, firm, prepared with calcium sulfate. Accessed at: http://ods.od.nih.gov/pubs/usdandb/Calcium-Content.pdf
57. Wu AH, Ziegler RG, Horn-Ross PL, et al.: Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol Biomarkers Prev 5:901–906, 1996.

58. Shu X, Zheng Y, Cai H, et al.: Soy food intake and breast cancer survival. JAMA 302:2437–2443, 2009.
59. Caan BJ, Natarajan L, Parker B, et al.: Soy food consumption and breast cancer prognosis. Cancer Epidemiol Biomarkers Prev 20:854–858, 2011.
60. Guha N, Kwan ML, Quesenberry CP Jr, Weltzien EK, Castillo AL, Caan BJ: Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat 118:395–405, 2009.
61. Adlercreutz H, Mazur W: Phyto-oestrogens and Western diseases. Ann Med 29:95–120, 1997.
62. Taylor CK, Levy RM, Elliott JC, Burnett BP: The effect of genistein aglycone on cancer and cancer risk: a review of in vitro, preclinical, and clinical studies. Nutr Rev 67:398–415, 2009.
63. Zhang X, Shu XO, Gao YT, et al.: Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. J Nutr 133:2874–2878, 2003.
64. Jenkins DJ, Kendall CW, Marchie A, et al.: Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. JAMA 290:502–510, 2003.
65. Koh WP, Wu AH, Wang R, et al.: Gender-specific associations between soy and risk of hip fracture in the Singapore Chinese Health Study. Am J Epidemiol 170:901–909, 2009.
66. McLaughlin JM, Olivo-Marston S, Vitolins MZ, et al.: Effects of tomato- and soy-rich diets on the IGF-I hormonal network: a crossover study of postmenopausal women at high risk for breast cancer. Cancer Prev Res (Phila) 4:702–710, 2011.
67. Arjmandi BH, Khalil DA, Smith BJ, et al.: Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. J Clin Endocrinol Metab 88:1048–1054, 2003.
68. Khalil DA, Lucas EA, Juma S, Smith BJ, Payton ME, Arjmandi BH: Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism. J Nutr 132:2605–2608, 2002.
69. World Cancer Research Fund and the American Institute for Cancer Research. "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*." Washington, DC: American Institute for Cancer Research, 2007.
70. Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A: Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. Cancer Epidemiol Biomarkers Prev 17:387–392, 2008.
71. Liu J, Wang J, Leng Y, Lv C: Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. Int J Cancer 133:473–485, 2013.
72. Wu QJ, Yang Y, Vogtmann E, et al.: Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies. Ann Oncol 24:1079–1087, 2013.
73. Lam TK, Gallicchio L, Lindsley K, et al.: Cruciferous vegetable consumption and lung cancer risk: a systematic review. Cancer Epidemiol Biomarkers Prev 18:184–195, 2009.
74. Wu QJ, Yang Y, Wang J, Han LH, Xiang YB: Cruciferous vegetable consumption and gastric cancer risk: a meta-analysis of epidemiological studies. Cancer Sci 104:1067–1073, 2013.
75. Eliassen AH, Hendrickson SJ, Brinton LA, et al.: Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 104:1905–1916, 2012.
76. Aune D, Chan DS, Vieira AR, et al.: Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat. 134:479–493, 2012.
77. Yang T, Yang X, Wang X, Wang Y, Song Z: The role of tomato products and lycopene in the prevention of gastric cancer: a meta-analysis of epidemiologic studies. Med Hypotheses 80:383–388, 2013.
78. Bertuccio P, Rosato V, Andreano A, et al.: Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. Ann Oncol. 24:1450–1458, 2013.
79. Zhou Y, Zhuang W, Hu W, Liu GJ, Wu TX, Wu XT: Consumption of large amounts of Allium vegetables reduces risk for gastric cancer in a meta-analysis. Gastroenterology 141:80–89, 2011.
80. Jana S, Mandlekar S: Role of phase II drug metabolizing enzymes in cancer chemoprevention. Curr Drug Metab 10:595–616, 2009.
81. Lenzi M, Fimognari C, Hrelia P: Sulforaphane as a promising molecule for fighting cancer. Cancer Treat Res 159:207–223, 2014.
82. Khan N, Afaq F, Mukhtar H: Apoptosis by dietary factors: the suicide solution for delaying cancer growth. Carcinogenesis 28: 233–239, 2007.
83. Hung HC, Joshipura KJ, Jiang R, et al.: Fruit and vegetable intake and risk of major chronic disease. J Natl Cancer Inst 96:1577–1584, 2004.
84. He FJ, Nowson CA, Lucas M, MacGregor GA: Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. J Hum Hypertens 21:717–728, 2007.
85. He FJ, Nowson CA, MacGregor GA: Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. Lancet 367: 320–326, 2006.
86. Whelton PK, He J, Appel LJ, et al.: Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. JAMA 288:1882–1888, 2002.
87. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ: Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ 341:c4229, 2010.
88. Cooper AJ, Forouhi NG, Ye Z, et al.: Fruit and vegetable intake and type 2 diabetes: EPIC-InterAct prospective study and meta-analysis. Eur J Clin Nutr 66:1082–1092, 2012.

Received August 16, 2013; revision accepted November 13, 2013.