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# Nutrition and cancer

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## Abstract

Evidence from both animal and epidemiologic studies indicate that throughout life excessive energy intake in relation to requirements increases risk of human cancer. Rapid growth rates in childhood lead to earlier age at menarche, which in turn increases risk of breast cancer, and accumulation of body fat in adulthood in related to cancers of the colon, kidney, and endometrium as well as postmenopausal breast cancer. Higher intake of vegetables and fruits has been associated with lower risks of many cancers. The constituents responsible for these apparent protective effects remain uncertain, although evidence supports a contribution of folic acid. Recent evidence suggests that the percentage of energy from fat in the diet is not a major cause of cancers of the breast or colon. Higher intake of meat and dairy products has been associated with greater risk of prostate cancer, which may be related to their saturated fat content. Also, red meat consumption has been associated with risk of colon cancer in numerous studies, but this appears to be unrelated to its fat content. Excessive consumption of alcohol increases risks of upper gastrointestinal tract and even moderate intake appears to increase cancers of the breast and large bowel. Although many details remain to be learned, evidence is strong that remaining physically active and lean throughout life, consuming an abundance of fruits and vegetables, and avoiding high intakes of red meat, foods high in animal fat, and excessive alcohol will substantially reduce risk of human cancer.

Key words: nutrition; neoplasms; review

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## Resumen

La evidencia que proporcionan tanto los estudios en animales como los epidemiológicos, indica que el consumo excesivo de energía incrementa el riesgo de cáncer en los humanos. Las tasas de crecimiento rápidas durante la niñez pueden conducir a una menarquia temprana, lo que aumenta el riesgo de cáncer de mama, y la acumulación de grasa corporal en la madurez está relacionada con el cáncer de colon, riñón y endometrio, y con el de mama después de la menopausia. Un alto consumo de verduras y frutas se ha relacionado con riesgos más bajos de contraer varios tipos de cáncer. Sigue sin conocerse cuáles son los componentes responsables de estos efectos, aparentemente protectores, aunque se le atribuye un papel importante al ácido fólico. En la dieta, el porcentaje de energía que proviene de la grasa no constituye una causa importante del cáncer de mama o de colon. El consumo excesivo de carne y de productos lácteos se ha asociado con un riesgo mayor de cáncer de próstata; esto se puede relacionar con su contenido de grasa saturada. De igual forma, en numerosos estudios la ingesta de carne roja se ha asociado con un mayor riesgo de cáncer de colon, aunque esto parece no estar relacionado con su contenido de grasa. El consumo excesivo de alcohol aumenta los riesgos de cáncer del tracto gastrointestinal superior, e incluso parece que su consumo moderado incrementa el riesgo de cáncer de mama y del intestino grueso. Aunque falta conocer muchos detalles, la información muestra que el mantenerse físicamente activo y delgado, consumir frutas y verduras en abundancia, y evitar la ingesta excesiva de carne roja, de alimentos ricos en grasa animal y el no abusar del alcohol, puede reducir substancialmente el riesgo de cáncer en los seres humanos.

Palabras clave: nutrición; neoplasmas; revisión

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Following cardiovascular disease, cancer is the second most important cause of death in most affluent countries and is increasingly important in developing countries as mortality from infectious diseases declines.[1,2] In the US, about one in three persons will be diagnosed with cancer during their lifetime and about 60% of those diagnosed will die of cancer.[3] Although overall cancer rates among adults vary only modestly around the world, the types of cancers are dramatically different.[1,2] In most affluent countries cancers of the lung, colon, breast, and prostate contribute most to incidence and mortality (see Figures 1a and 1b). In poorer regions and the Far East, cancers of the stomach, liver, oral cavity, esophagus, and uterine cervix are most important. In Japan, for example, rates of breast cancer have until recently been only about one fifth those of the US and the differences in rates of colon and prostate cancers have been even greater.[5] However, cancer incidence rates are very dynamic; many areas of the world are experiencing a transition from the cancer incidence patterns of poorer to those of affluent areas.[1] In almost all countries rates of breast cancer have been increasing.

Although the development of cancer is characterized by alterations in DNA and some of these changes can be inherited, inherited mutations cannot account for the dramatic differences in cancer rates seen around the world. Populations that move from countries with low rates of cancer to areas with high rates, or the reverse, almost invariably achieve the rates characteristic of the new homeland.[6-8] The rate of change can vary, though, from several decades in the case of colon cancer, to about three generations for breast cancer.[8-11] The dramatic changes in cancer rates within a countries provide further evidence for the importance of noninherited factors. For example, in Japan rates of colon cancer mortality increased about 2.5-fold between 1950 and 1985.[5]

The dramatic variations in cancer rates around the world and changes over time imply that these malignancies are potentially avoidable if we were able to know and alter the causal factors. For a few cancers, such as lung cancer, the primary causes are well known, in this case smoking, but for most others the etiologic factors are less well established. However, there are strong reasons to suspect that dietary and nutritional factors may account for many of these variations in cancer rates. First, a role of diet has been suggested by observations that national rates of specific cancers are strongly correlated with aspects of diet such as per capita consumption of fat.[12] Also, numerous studies in animals, including a series of detailed experiments conducted during the 1930's.[13] clearly demonstrated that dietary manipulations could dramatically influence tumorigenesis.

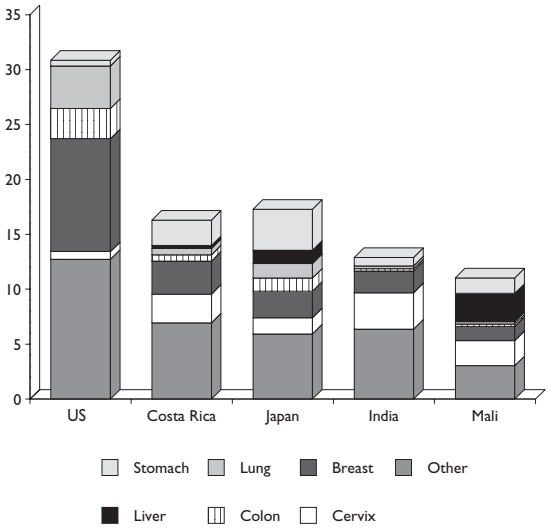


**FIGURE 1A. CANCER INCIDENCE RATES FOR MEN IN SEVERAL COUNTRIES.[2,4] CUMULATIVE INCIDENCE 0-74 YEARS (PER 100,000 POPULATION). (US-SEER-NATIONWIDE, COSTA RICA-NATIONWIDE, JAPAN-OSAKA, INDIA-BANGALORE, MALI-BAMAKO) (SKIN CANCERS NOT INCLUDED)**

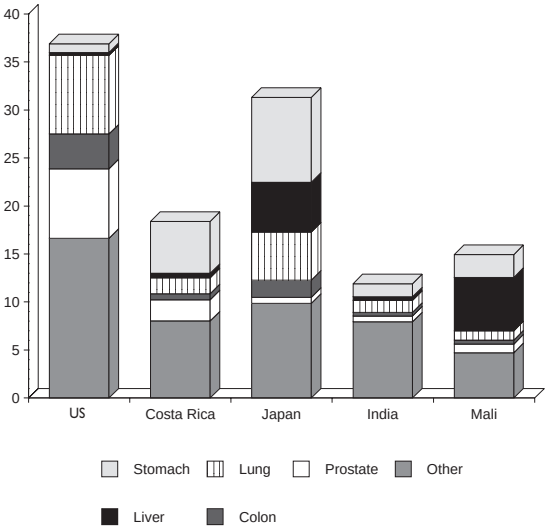


**FIGURE 1B. CANCER INCIDENCE RATES FOR WOMEN IN SEVERAL COUNTRIES.[2,4] CUMULATIVE INCIDENCE 0-74 YEARS (PER 100,000 POPULATION). (US-SEER-NATIONWIDE, COSTA RICA-NATIONWIDE, JAPAN-OSAKA, INDIA-BANGALORE, MALI-BAMAKO) (SKIN CANCERS NOT INCLUDED)**

Also, a multitude of steps in the pathogenesis of cancer have been identified where dietary factors could plausibly act either to increase or decrease the probability that the clinical cancer will develop. For example, carcinogens in food can directly damage DNA and other dietary factors may block the endogenous synthesis of carcinogens or induce enzymes involved in the activation or deactivation of exogenous carcinogenic substances.[14] Oxidative damage to DNA is likely to be an important cause of mutations and can potentially be enhanced by some dietary factors, such as polyunsaturated fats, or reduced by dietary antioxidants or nutrients that are co-factors for antioxidant enzymes, such as selenium or copper.[15] Inadequate intake of dietary factors needed for DNA synthesis, such as folic acid, could also influence the risk of mutation. The rate of cell division will influence whether DNA lesions are replicated and is thus likely to influence the probability of cancer developing.[15] Thus, energy balance and growth rates, which can be influenced by a variety of essential nutrients, could affect cancer rates. Dietary factors can influence endogenous hormone levels, including estrogens and various growth factors, which can influence cell cycling and, thus, potentially cancer incidence. Estrogenic substances found in some plant foods can also interact with estrogen receptors and thus could either mimic or block the effects of endogenous estrogens.[14] Many other aspects of diet can alter cell proliferation or differentiation either by direct hormonal effects, such as by vitamins A or D, or indirectly by influencing inflammatory or irritative processes, such as specific fatty acids that are precursors of prostaglandins or that inhibit their synthesis. Many other examples can be given by which dietary factors could plausibly influence the development of cancer.[14,15]

## Epidemiologic investigation of diet and cancer relationships

The strong suggestions from international comparisons, animal studies, and mechanistic investigations that various aspects of diet might importantly influence risk of cancer raises the two critical sets of questions: Which dietary factors are actually important determinants of human cancer? What is the nature of the dose-response relationships? The nature of the dose-response relationships is particularly important because a substance could be carcinogenic to humans, but there could be no important risk within the range of intakes actually consumed by humans. Alternatively, another factor could be critical for protection against cancer, but all persons in a population may already be consuming sufficient amounts to receive the maximal benefit. In either case, there is no potential for reduction in cancer rates by altering current intakes. The important factors to identify are those for which at least some part of the population is either consuming a toxic level or is not eating a sufficient amount for optimal health.

A variety of epidemiologic approaches can be used to investigate diet and human cancer relationships, including case-control or cohort studies and randomized trials. Relationships between diet, nutrition, and cancer incidence in epidemiologic studies can be evaluated by collecting data on dietary intake, by using biochemical indicators of dietary factors, or by measuring body size and composition. Food frequency questionnaires have been used to assess diet in most epidemiologic studies because they provide information on usual diet over an extended period of time and are sufficiently efficient to be used in large populations. Food frequency questionnaires have been shown to be sufficiently valid to detect important diet-disease relationships in comparisons with more detailed assessments of diet and biochemical indicators.[16] Biochemical indicators of diet can be useful in some situations, but for many dietary factors of interest, such as total fat, fiber, and sodium, no useful indicators exist. DNA specimens have been collected from participants in many studies and allow the examination of gene-diet interactions. Until now, most information on diet and cancer has been obtained from case-control studies. However, a number of large prospective cohort studies of diet and cancer in various countries are now ongoing and will be producing reliable data at an exponentially increasing rate as the their populations age.

Epidemiologic investigations should be viewed as complementary to animal studies, in vitro investigations, and metabolic studies of diet in relation to intermediate endpoints, such as hormone levels. Although conditions can be controlled to a much greater degree in laboratory studies than in free living human populations, the relevance of findings to humans will always be uncertain, particularly in regard to dose-response relationships. Ultimately, our knowledge is best based on a synthesis of epidemiologic, metabolic, animal, and mechanistic studies.

## Current state of knowledge for specific aspects of diet

Diet is a complex composite of various nutrients and nonnutritive food constituents and there are many types of human cancer, each with its own pathogenet-

ic mechanisms; thus the combinations of specific dietary factors and cancer is almost limitless. This brief overview will focus primarily on cancers that are most important in affluent populations and that are rapidly increasing in countries undergoing economic transition. Aspects of diet for which there are strong hypotheses and substantial epidemiologic data are also emphasized.

*Energy balance, growth rates, and body size*

Studies by Tannenbaum and colleagues[13,17] during the first half of the 20th century indicated that energy restriction could profoundly reduce the development of mammary tumors in animals. This finding has been consistently replicated in a wide variety of mammary tumor models and has also been observed for a wide variety of other tumors.[18-22] For example, restriction in energy intake by approximately 30% can reduce mammary tumors by as much as 90%.[23] The possibility that this relationship, which is the most consistent and strong effect of diet in animal studies, might also apply to humans has received relatively little attention until recently.

The most sensitive indicators of the balance between energy intake and expenditure are growth rates and body size, which can be measured well in epidemiologic investigations, although they also reflect genetic and other nonnutritional factors. Adult height can thus provide an indirect indicator of pre-adult nutrition and adult weight gain and obesity reflect positive energy balance later in life. Internationally, the average national height of adult women is strongly associated with risk of breast cancer.[24] Also, in case-control and cohort studies, greater height has generally been associated with an increased risk of breast cancer.[25] For example, in a representative US sample, taller women had nearly twice the risk of breast cancer compared to the shortest.[26] Taller height has also been associated with risk of colon and other cancers.[27,28] In populations who were traditionally short, such as the Japanese, rapid gains in height during the last several decades[29] have corresponded with increases in breast cancer rates. Further support for an important role of growth rates comes from epidemiologic studies of age at menarche. An early menarche is a well-established risk factor for breast cancer. The difference in the late age in China, approximately 17 years,[30] compared to 12 and 13 years of age in the US,[31] contributes importantly to differences in breast cancer rates between these populations. Body mass index, height, and weight have consistently been strong determinants of age at menstruation,[32-34] but the composition of diet appears to have little if any effect. Collectively, these studies provide strong evidence, consistent with animal experiments, that rapid growth rates prior to puberty play an important role in determining future risk of breast and probably other cancers. Whether the epidemiologic findings are due only to restriction of energy intake in relation to requirements for maximal growth, or whether the limitation of other nutrients, such as essential amino acids, may also play a role cannot be determined from available data.

A positive energy balance during adult life and the resultant accumulation of body fat also contributes importantly to several human cancers. The best established relationships are with cancers of the endometrium and gall bladder.[35-39] Greater adiposity also increases the risk of colon cancer in both women[40] and men, particularly when assessed as abdominal circumference.[41] The relation between body fatness and breast cancer is more complex. Prior to menopause, women with greater body fat have reduced risks of breast cancer,[42,43] and after menopause a positive, but weak, association with adiposity is seen. These findings are probably the result of anovulatory menstrual cycles in fatter women prior to menopause,[44] which should reduce risk, and the synthesis of endogenous estrogen by adipose tissue in postmenopausal women,[45] which is presumed to increase risk of breast cancer.

*Dietary fat and meat intake*

In the landmark 1982 National Academy of Sciences review of diet, nutrition and cancer,[46] reduction in fat intake to 30% of calories was the primary recommendation; this objective has been echoed in subsequent dietary recommendations as well.[47,48]

Interest in dietary fat as a cause of cancer began in the first half of the 20th century when studies by Tannenbaum and colleagues,[13,17] indicated that diets high in fat could promote tumor growth in animal models. In this early work, energy (caloric) restriction also profoundly reduced the incidence of tumors. A vast literature on dietary fat and cancer in animals has subsequently accumulated (reviewed elsewhere).[22,46,49-51]

Dietary fat has a clear effect on tumor incidence in many models, although not in all;[52,53] however, a central issue has been whether this is independent of the effect of energy intake. An independent effect of fat has been seen in some animal models,[22,49,50] but this has been either weak[54] or nonexistent[23] in some studies designed specifically to address this issue. A possible relation of dietary fat intake to cancer incidence has also been hypothesized because the large international differences in rates of cancers of the breast, colon, pros-

tate, and endometrium are strongly correlated with apparent *per capita* fat consumption.[12,55,56] These correlations are limited to animal, not vegetable, fat.[57]

Fat and breast cancer

Although a major rationale for the dietary fat hypothesis has been the international correlation between fat consumption and national breast cancer mortality,[12] in a study of 65 Chinese counties,[58] in which per capita fat intake varied from 6 to 25 percent of energy, only a weak positive association was seen between fat intake and breast cancer mortality. Notably, five counties consumed approximately 25% of energy from fat, yet experienced rates of breast cancer far below those of US women with similar fat intake,[59] thus providing strong evidence that factors other than fat intake account for the large international differences. Breast cancer incidence rates have increased substantially in the United States during this century, as have the estimates of per capita fat consumption based on food disappearance data. However, surveys based on reports of individual actual intake, rather than food disappearance, indicate that consumption of energy from fat, either as absolute intake or as a percentage of energy, has actually declined in the last several decades,[60,61] a time during which breast cancer incidence has increased.[62]

A substantial body of data from prospective cohort studies is now available to assess the relation between dietary fat intake and breast cancer in developed countries. In a pooled analysis of the prospective studies with more than 200 cases of breast cancer,[63] no overall association was seen for overall fat intake over the range of <20 to >45% of energy from fat (see Figure 2). A similar lack of association was seen among postmenopausal women only and for specific types of fat. Only among the small number of women consuming less than 15% of energy from fat was a significant association seen; breast cancer risk was elevated two-fold in this group.

Although total fat intake has been unrelated to breast cancer risk in prospective epidemiologic studies, there is some evidence that the type of fat may be important. In animal mammary tumor models, the tumor promoting effect of fat intake has been observed primarily for polyunsaturated fats when fed in the presence of high fat diets containing approximately 45% of energy.[64,65] However, in a meta-analysis of case-control studies,[66] increased risk of breast cancer was somewhat greater for saturated (relative risk= 1.46) and monounsaturated fats (relative risk = 1.41) than for polyunsaturated fats (relative risk = 1.25). In data based

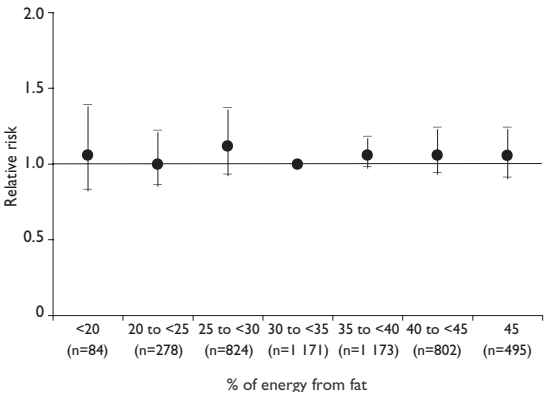


**FIGURE 2. POOLED RELATIVE RISKS AND 95 PERCENT CONFIDENCE INTERVALS FOR VARIOUS LEVELS OF ENERGY FROM FAT. A LEVEL OF 30 TO LESS THAN 35 PERCENT OF TOTAL ENERGY FROM FAT WAS DESIGNATED AS THE REFERENCE CATEGORY. N DENOTES THE NUMBER OF CASES IN EACH CATEGORY. [63]**

on the detailed food frequency questionnaire administered in 1984 in the Nurses' Health Study, an inverse association between monounsaturated fat and breast cancer was present.[59] This is an intriguing observation given the relatively low rates of breast cancer in Southern European countries which have high average intakes of monounsaturated fats due to the use of olive oil as the primary fat. In case-control studies in Spain and Greece, women who used more olive oil had reduced risks of breast cancer.[67,68] Furthermore, olive oil has been shown to be protective relative to other sources of fats in some animal studies.[49]

Fat and colon cancer

In comparisons among countries, rates of colon cancer are strongly correlated with national *per capita* disappearance of animal fat and meat, with correlation coefficients ranging between 0.8 and 0.9.[12,57] Based on these epidemiologic investigations and animal studies, a hypothesis has developed that dietary fat increases excretion of bile acids, which can be converted to carcinogens or promoters.[69] However, recent evidence from many studies that higher levels of physical activity reduce risk of colon cancer risk means that at least part of the high rates in affluent countries previously attributed to fat intake are probably due to sedentary lifestyle.

With some exceptions,[70-73] case-control studies have generally shown an association between risk of colon cancer and intake of fat[74-81] or red meat.[82-87]

However, in many of these studies, a positive association between total energy intake and risk of colon cancer has also been observerved,[74-78,80,81] raising the question of whether it is general overconsumption of food or the fat composition of the diet that is etiologically important. A recent meta-analysis by Howe and colleagues of 13 case-control studies found a significant association between total energy and colon cancer, but saturated, monounsaturated and polyunsaturated fat were not associated with colon cancer independently of total energy.[88]

The relation between diet and colon cancer has been examined in several large prospective studies. These have not confirmed the positive association with total energy intake in case-control studies,[89-93]suggesting that the case-control studies were distorted by reporting bias. The Nurses' Health Study showed about a 2-fold higher risk of colon cancer among women in the highest compared to those in the lowest quintile of animal fat intake.[89]In a multivariate analysis of these data, which included red meat and animal fat intakes in the same model, red meat intake remained significantly predictive of risk of colon cancer, whereas the association with animal fat was eliminated. A cohort study from the Netherlands showed a significant direct association between intake of processed meats and risk of colon cancer, but no relationship was observed for fresh meats or overall fat intake.[90] A cohort study in Iowa women also found a direct association with processed meats, although this was not statistically significant.[91] Among a large cohort study of men, a direct association between red meat consumption and risk of colon cancer was seen, but no association was observed with other sources of fat.[92] In this study, no overall relationship existed between total or saturated fat and colon cancer despite a substantial range in fat intake. A similar association was noted for colorectal adenomas in the same cohort of men.[69] In the large American Cancer Society Cohort,[93] little relation was seen between either meat or fat intake and mortality due to colon cancer, but the dietary questionnaire was brief and of uncertain validity. The apparently stronger association with red meat compared with fat in several recent cohort studies needs further confirmation, but could result if the fatty acids or nonfat components of meat (for example the heme iron or carcinogens created by cooking) were the primary etiologic factors. This issue does have major practical implications as current dietary recommendations[94] support the daily consumption of red meat as long as it is lean.

## Fat and prostate cancer

Associations with fat intake have been seen in many case-control studies,[95-105] but sometimes only in subgroups. In a recent large case-control study among various ethnic groups within the US,[106] consistent associations with prostate cancer risk were seen for saturated fat, but not with other types of fat.

The association between fat intake and prostate cancer risk has been assessed in only a few cohort studies. In a cohort of 8 000 Japanese men living in Hawaii, no association was seen between intake of total or unsaturated fat.[107] However, diet was assessed with a single 24-hour recall in this study so the lack of association may not be informative. In a study of 14 000 Seventh-Day Adventist men living in California, a positive association between the percentage of calories from animal fat and prostate cancer risk was seen, but this was not statistically significant.[108] More recently two large prospective studies have been published. In the Health Professionals Follow-up Study of 51 000 men, a positive association was seen with intake of red meat, total and animal fat, which was largely limited to aggressive prostate cancers.[109] No association was seen with vegetable fats. In another cohort from Hawaii, increased risks of prostate cancer were seen with consumption of beef and animal fat.[110]

Although further data are desirable, the evidence from international correlations, case-control, and cohort studies is reasonably consistent in support of an association between consumption of fat-containing animal products and prostate cancer incidence. This evidence does not generally support a relation with intake of vegetable fat, which suggests that either the type of fat or other components of these animal products are responsible. Evidence also suggests that animal fat consumption may be most strongly associated with aggressive prostate cancer, which suggests an influence on the transition from the wide-spread indolent form to the more lethal form of this malignancy.

## Other cancers

Rates of other cancers that are common in affluent countries, including those of the endometrium and ovary, are, of course, also correlated with fat intake internationally. Although these have been studied in a small number of case-control investigations, consistent associations with fat intake have not been seen.[111-120] In a prospective study among Iowa women,[121] no evidence of relation between fat intake and risk of

endometrial cancer was observed. Positive associations have been hypothesized between fat intake and risks of skin cancer[122] and lung cancer, but relevant data in humans are limited.

Summary of fat and cancer

As the findings from large prospective studies have become available, support for a major relationship between fat intake and breast cancer risk has weakened considerably. For colon cancer, the associations seen with animal fat internationally have been supported in numerous case-control and cohort studies. However, more recent evidence has suggested that this might be explained by factors in red meat other than simply its fat content. Further, the importance of physical activity as a protective factor against colon cancer indicates that international correlations probably overstate the contribution of diet to differences in colon cancer incidence. The available evidence most strongly supports an association between animal fat consumption and risk of prostate cancer, particularly the aggressive form of this disease. As with colon cancer, however, the possibility remains that other factors in foods containing animal fat contribute to risk.

*Fruits and vegetables*

A massive body of epidemiologic data indicates that higher consumption of fruits and vegetables is associated with a reduced risk of cancers at many sites. Inverse relationships with intake of these foods have been observed in over 200 case-control and prospective cohort studies[123,124] and additional support comes from studies in which biochemical indicators of fruit and vegetable consumption, such as serum carotenoid levels, are also associated with reduced risks. The studies are particularly numerous and consistent for cancers of the lung[125] and stomach;[126] inverse associations have also been observed in many case-control studies of colon cancer but prospective data are still limited. Somewhat fewer studies have also indicated inverse associations with cancers of the oral cavity, larynx, esophagus, endometrium, cervix, bladder, kidney and breast.[127] Although, inverse associations have not been seen between fruit and vegetable consumption in general and risk of prostate cancer, inverse associations with tomato products, the primary source of the carotenoid lycopene, have been seen in several case-control and prospective studies.[99,108,128]

Although the evidence that high consumption of fruits and vegetables can reduce the risk of many cancers is strong, the constituents of these foods that are responsible for these reduced risks are less clear. These foods contain a myriad of biologically active chemicals, including both recognized nutrients and many more nonnutritive constituents, that could potentially play a role in protection against cancer.[14] Among the potentially protective factors are various carotenoids, folic acid, vitamin C, phytoestrogens and fiber (discussed below). The identification of the specific protective constituents, or combination of constituents, is a daunting task and may never be completely possible. Further details on the types and amounts of fruits and vegetables that appear to be particularly protective could provide additional practical guidance for those wanting to select an optimally healthy diet.

*Dietary fiber and cancer risk*

Interest in dietary fiber is largely the result of Dr. Denis Burkitt's observation of low rates of colon cancer in areas of Africa where fiber consumption and stool bulk were high.[129] Although fiber was originally seen simply as providing bulk to dilute potential carcinogens and speed their transit through the colon, other hypotheses have suggested that fiber may act by binding carcinogenic substances,[130] altering the colonic flora,[131-134] reducing the pH,[135] or serving as the substrate for the generation of short-chain fatty acids that are the preferred substrate for colonic epithelial cells.[136]

As epidemiologic evidence has accrued, the importance of dietary fiber in reducing risk of colon cancer has become less clear. First, the populations with high fiber consumption and low intakes rates of colon cancer are also typically those of poorer countries where consumption of meat and obesity are low and physical activity is high. Evidence has become clearer that each of these factors reduces risk and thus is likely to explain at least part of the ecological associations between low intake of dietary fiber and colon cancer rates. Also, in case-control studies, intake of cereal products or fiber from grains has not usually been associated with reduced risks of colon cancer, in contrast to the abundant evidence for a protective effect of fruits and vegetables.[137,138] Indeed, in some studies higher consumption of grains has been associated with greater risks of colon cancer.[70,83,139,140] Also, in several large prospective studies, even overall fiber intake has not been clearly associated with lower risk of colon cancer incidence after adjustment for other risk factors.[89-92] Thus, fiber intake does not appear to account for the reduced risk of colon cancer associated with consumption of fruits and vegetables, and evidence supporting higher consumption of grain fiber to reduce risk of colon cancer is weak.

Higher intake of fiber has also been hypothesized to reduce risk of breast cancer by interrupting the enterohepatic circulation of estrogens.[141] However, in prospective studies, little or no relationship has been observed between fiber intake and risk of breast cancer.[59,142,143]

*Alcoholic and caffeinated beverages*

High consumption of alcohol, particularly in combination with cigarette smoking, is a well-established cause of cancer of the oral cavity, larynx, esophagus, and liver.[144] More recently, substantial evidence from case-control and cohort studies indicates that amounts as low as one or two drinks per day increase risk of breast cancer.[145,146] Moderate alcohol consumption appears to increase endogenous estrogen levels, which may account for this effect.[45,147,148] Moderate alcohol consumption also appears to be associated with risk of cancers of the colon and rectum.[138] Alcohol interferes with the availability of folic acid, which may account for its relation with large bowel cancers.[149-151]

Coffee contains multiple mutagenic substances[15] and concern has thus existed that it might be an important cause of cancer in humans. Although early evidence suggested a possible positive association with pancreatic cancer, this has not been supported in most subsequent studies.[152-154] Similarly, for breast cancer, coffee consumption has been unassociated[155] or even weakly inversely associated with risk.[156] Green tea contains polyphenolic compounds that inhibit tumors in experimental animals[157] and inverse associations between green tea consumption and risk of gastric cancer have been seen in case-control studies from Japan[158] and China.[159] Notably, however, rates of gastric cancer in the US, where tea consumption is low, are among the lowest in the world; this has been attributed in part to relatively low salt intake.[126]

*Vitamin supplements*

Relatively little data are available on vitamin supplement use and cancer incidence. High-dose supplements of vitamins C and E have not been associated with reductions in breast cancer incidence.[142,160] In the study by Hunter, there was a suggestion that vitamin A supplements at the RDA level might be associated with reductions in breast cancer risk among women whose dietary intakes were relatively low, but higher intakes did not confer additional reductions in risk. Limited data suggest that folic acid contained in multiple vitamins might reduce risk of large bowel cancer,[149,150] but this needs confirmation. In a single case-control study, vitamin E supplements were associated with a reduced risk of oral cancer.[161] In a randomized trial conducted in a region of China with low consumption of fruits and vegetables, a supplement containing beta-carotene, vitamin E, and selenium reduced incidence of stomach cancer.[162] Although further research is needed, on the basis of available evidence, the prevention of cancer does not provide justification for the use of vitamin supplements by most persons with a reasonable diet.

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