Cancer Chemoprevention With Nuts

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It is well established that increased nut consumption is associated with a reduced risk of major chronic diseases, such as cardiovascular disease and type 2 diabetes mellitus. On the other hand, the association between nut consumption and cancer mortality is less clear. Recent studies have suggested that nut consumption is associated with reduced cancer mortality. This evidence reinforces the interest to investigate the chemopreventive properties of nuts, and it raises questions about the specific cancer type(s) and setting that can be more affected by nut consumption, as well as the cellular mechanisms involved in this protective effect. Here we discuss recent studies on the association of nut consumption and cancer, and we propose specific cellular mechanisms by which nut components can affect cancer progression.

In the last four years, there has been a consistent rise in the number of diagnosed cancer cases and cancer deaths worldwide. According to the 2012 World Health Organization data on cancer incidence in the global population, more than 14 million cases were diagnosed compared to 12.7 million in 2008 and 8.2 million deaths were recorded compared to 7.6 million in 2008 (1–2). More worryingly, it has been predicted that cancer cases will increase to more than 19 million a year by 2025.

The reasons for these soaring numbers have been identified primarily in the increased average life span, lack of prevention, diagnoses, and adequate treatment in developing countries, and changes in lifestyle occurring in developing nations, where obesity and smoking habits are catching up with industrialized countries’ rates. Chemoprevention and early diagnosis are going to be pivotal to counteract this looming trend (3–4).

It is now well established that lifestyle habits have an impact in the development of several human cancers (5–6). It has been estimated that up to 40% of cancer cases are linked to unhealthy lifestyle habits such as smoking, being overweight, alcohol consumption, low fruit and vegetable intake, occupational hazards, and exposure to sun and sunbeds. Therefore, there is currently a huge interest in studying the impact of lifestyle changes on cancer development and progression. Diet in particular has received increasing attention, with the identification of food that could either increase or reduce the risk of developing specific types of cancer (7). For instance, it has been estimated that a Mediterranean diet rich in fruits, vegetables, fish, and olive oil could reduce the risk of cancer by 12%, supporting the conclusion that dietary changes could be highly beneficial in cancer prevention (8–9).

In the past few years, an inverse correlation between nut consumption and major chronic diseases such as cardiovascular diseases, metabolic syndrome, and type 2 diabetes has been established (10–14). In addition, studies have suggested that nut consumption could also have a chemopreventive effect, especially on colorectal and prostate cancer (15–16). Recent epidemiological studies have confirmed an inverse association between frequent nut consumption and cancer mortality (17–19). Questions still remain on the specific cellular mechanisms and the specific cancer types that are more likely to benefit from this effect (20–22). In this review we will discuss recent studies on the association of nut consumption and risk of cancer, and we will suggest specific cellular mechanisms by which nut components could affect cancer progression.

The Tree Nuts and Nut Composition

By definition, a nut is a dry fruit consisting of a hard or tough shell around an edible kernel. Walnuts (Juglans regia), hazelnuts (Corylus avellana), macadamias (Macadamia integrifolia), pecans (Carya illinoiensis), almonds (Prunus amygdalus), cashews (Anacardium occidentale), and pistachios (Pistacia vera) are all tree nuts; Brazil nuts (Bertholletia excelsa) are seeds but share the same properties of nuts, and so do peanuts (Arachis hypogaea), which are botanically legumes but are frequently grouped with nuts because of their similar nutritional properties. Chestnuts (Castanea) are an exception, as they contain a high amount of starch and little fat and are therefore considered nutritionally dissimilar even if they are tree nuts (23).

Nuts have a high total fat content, ranging from 46% in cashews to 76% in macadamia nuts, making them the richest natural plant foods in fat after vegetable oils (23). However, nuts mainly contain monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA) and a very low content of saturated fatty acids (SFA), ranging from 4% to 16%. The percentage of MUFA and PUFA varies between different types of nuts: many nuts contain mostly MUFA (mainly oleic acid). Brazil nuts have similar proportions of...
MUFA and PUFA, whereas walnuts contain mainly PUFA, both linoleic acid and α-linolenic acid (23). Nuts also contain proteins, ranging from 7.9 g in macadamia nuts to 25.8 g in peanuts (per 100 g) and often possess high levels of L-arginine, which is a precursor of nitric oxide (23). Dietary fiber in nuts also ranges from 3.7 g in pine nuts to 10.4 g in hazelnuts (per 100 g). Importantly, nuts are enriched in several phytochemicals and indeed their beneficial effects have been largely ascribed to the simultaneous presence of these micronutrients, as described below. Amongst the other micronutrients, nuts contain the B-vitamin folate, ranging from 22 μg in pecans and Brazil nuts to 145 μg in peanuts (per 100 g), as well as antioxidant vitamins (tocopherols) and phenolic compounds (23). Almonds are particularly rich in α-tocopherol, while walnuts are enriched in γ-tocopherol. Finally, nut composition comprises minerals such as calcium, magnesium, potassium, and selenium, while containing very low sodium concentrations.

**Nut Consumption and Mortality**

Association between nut consumption and total and cause-specific mortality has been recently investigated in a study (17) comprising 76,464 women from the Nurse's Health Study (NHS) and 42,498 men from the Health Professionals Follow-Up Study (HPSFS). This study revealed a statistically significant inverse correlation between frequent nut consumption and total mortality among women and men (Table 1). The inverse association remained mainly unchanged after exclusion of participants who had never smoked, or with extremely high or low body mass index (BMI), or with diabetes at baseline and after other adjustments. Furthermore, the inverse association persisted in all subgroups in analyses stratified by other potential risk factors for death, with stronger association observed among overweight or obese participants. Although the authors acknowledged potential limitations, including the fact that nut intake was self-reported or the restriction of the study sample to health professionals, this prospective study included a very large sample, 30 years of follow-up, repeated assessment of diet and lifestyle variables and data on more than 27,000 deaths for analysis. It is worth mentioning that this study was conducted in a non-Mediterranean population, which statistically consumes less nuts compared to the European population, and it is also less likely to follow a Mediterranean diet.

This inverse association has been further confirmed by a recent study conducted as an observational cohort of the PREDIMED trial to determine the potential association between total mortality, cardiovascular mortality, or cancer mortality and nut consumption, using baseline nut consumption as the exposure (18). The PREDIMED was a multicenter trial conducted in Spain for the primary prevention of cardiovascular events (24). Participants at high risk but with no cardiovascular disease at enrollment were assigned to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (participants were advised to reduce dietary fat). While results of the original trial are discussed later in this review, the recent longitudinal cohort study (18) determined that, in fully adjusted models, participants who ate more than three servings of nuts per week had a 39% reduction in total mortality risk compared with those who never or rarely ate nuts (hazard ratio [HR] = 0.61, 95% confidence interval [CI] = 0.45 to 0.83, \( P_{\text{trend}} = .012 \)). Interestingly, the reduction in total mortality risk increased up to 63% (CI = -34% to -78%) in participants who were in the upper category of nut consumption before the trial and were allocated to the diet supplemented with nuts during the trial.

Taken together, results from these studies support the conclusion of an inverse association between nut consumption and total mortality. Additional studies are now required to determine more specifically the role of different types of nuts, regular quantities to be consumed, and their potential interaction with other nutrients.

### Table 1. Hazard ratios for deaths compared with participants who did not eat nuts (17)

<table>
<thead>
<tr>
<th>Frequency of nut consumption</th>
<th>Multivariable-adjusted HRs (95% CI)</th>
<th>( P_{\text{trend}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 per week</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>1 per week</td>
<td>0.93 (0.90 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>2 to 4 times per week</td>
<td>0.89 (0.86 to 0.93)</td>
<td></td>
</tr>
<tr>
<td>5 or 6 times per week</td>
<td>0.87 (0.83 to 0.90)</td>
<td></td>
</tr>
<tr>
<td>7 or more times per week</td>
<td>0.85 (0.79 to 0.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.80 (0.73 to 0.86)</td>
<td></td>
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<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>&lt; 1 per week</td>
<td>0.84 (0.78 to 0.90)</td>
<td></td>
</tr>
<tr>
<td>1 per week</td>
<td>0.83 (0.76 to 0.89)</td>
<td></td>
</tr>
<tr>
<td>2 to 4 times per week</td>
<td>0.79 (0.73 to 0.86)</td>
<td></td>
</tr>
<tr>
<td>5 or more times per week</td>
<td>0.75 (0.62 to 0.94)</td>
<td></td>
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<tr>
<td>Heart disease</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>&lt; 1 per week</td>
<td>0.84 (0.77 to 0.91)</td>
<td></td>
</tr>
<tr>
<td>1 per week</td>
<td>0.78 (0.71 to 0.86)</td>
<td></td>
</tr>
<tr>
<td>2 to 4 times per week</td>
<td>0.75 (0.68 to 0.82)</td>
<td></td>
</tr>
<tr>
<td>5 or more times per week</td>
<td>0.71 (0.63 to 0.81)</td>
<td></td>
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<tr>
<td>Cancer</td>
<td></td>
<td>.03</td>
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<tr>
<td>&lt; 1 per week</td>
<td>0.93 (0.88 to 0.98)</td>
<td></td>
</tr>
<tr>
<td>1 per week</td>
<td>0.93 (0.87 to 1.00)</td>
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<tr>
<td>2 to 4 times per week</td>
<td>0.92 (0.85 to 0.98)</td>
<td></td>
</tr>
<tr>
<td>5 or more times per week</td>
<td>0.89 (0.81 to 0.99)</td>
<td></td>
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</tbody>
</table>

* Statistical tests were two-sided, and \( P \)-values were calculated with the use of the Wald test. HR = hazard ratio.
and demographic risk factors. In the study analyzing results from the NHS and HPFS studies (17), a similar inverse association was detected for consumption of two or more servings per week of peanuts or tree nuts (pooled multivariable-adjusted HR = 0.88, CI = 0.84 to 0.93 for peanuts; HR = 0.83, CI = 0.79 to 0.88 for tree nuts). Similarly, in the cohort of the PREDIMED study, reduced mortality risk was detected in participants who ate more than three servings per week of walnuts (HR, fully adjusted model = 0.55, CI = 0.40 to 0.76, \( P_{\text{trend}} < .001 \)) or other nuts, excluding walnuts (HR, fully adjusted model = 0.66, CI = 0.46 to 0.93, \( P_{\text{trend}} = .031 \)). Additional studies are urgently needed to investigate more in details the potential role of specific types of nuts.

**Nut Consumption, Cardiovascular Disease, and Other Diseases**

Several studies have now established the inverse correlation between nut consumption and risk of coronary heart disease (CHD) (25). Indeed, evidence supporting a protective role of nuts was so compelling that it led the US Food and Drug Administration to issue a health claim for nut consumption because of its link with reduced risk of cardiovascular diseases. A pooled analysis of four prospective studies conducted in the United States on healthy individuals with follow-up ranging from 6 to 18 years reported a 37% reduction in risk of fatal CHD (relative risk [RR] = 0.63, 95% CI = 0.51 to 0.83) in participants with the highest nut intake after multivariate adjustment (13). The Physicians’ Health Study in particular reported a 47% reduced risk of sudden cardiac death (RR = 0.53, 95% CI = 0.30 to 0.92) in subjects who ate nuts two or more times per week compared with those who never or rarely consumed them (26). The beneficial effect of nuts was independent of age, sex, BMI, alcohol use, or presence of cardiovascular risk factors. Results from the PREDIMED trial (24) further showed reduced risk of major cardiovascular events with a relative risk reduction of approximately 30% (multivariable-adjusted HR = 0.70, CI = 0.54 to 0.92, \( P = .01 \) for the group assigned to the Mediterranean diet with extra-virgin olive oil and HR = 0.72, CI = 0.54 to 0.96, \( P = .03 \) for the group assigned to the Mediterranean diet supplemented with nuts). In a fully adjusted analysis, statistically significant results were found for the combined cardiovascular end point and for stroke, but not for myocardial infarction alone (24). Although this study had several limitations, including losses to follow-up and the fact that the protocol was changed halfway through the trial, it was consistent with epidemiological studies showing an inverse association between the Mediterranean diet and incident stroke (27–28). These results have been further supported by the two recent studies mentioned in the previous paragraph. A more selective analysis of cause-specific mortality in the study by Bao et al. (17) revealed a statistically significant inverse association between nut consumption and deaths related to cardiovascular and heart disease in the pooled analysis of women and men (Table 1). Similarly, in the longitudinal cohort study of the PREDIMED trail (18), a reduced risk of cardiovascular mortality was observed in participants who ate more than three servings per week of walnuts (HR, fully adjusted model = 0.53, CI = 0.29 to 0.98, \( P_{\text{trend}} = .047 \)) or other nuts, excluding walnuts (HR, fully adjusted model = 0.42, CI = 0.20 to 0.89, \( P_{\text{trend}} = .031 \)).

Results from epidemiological studies spurred a wave of clinical studies to identify the mechanisms of the beneficial effects of nut consumption. Several studies have compared the effects of diets enriched in nuts and isoenergetic diets on serum lipids and lipoproteins. A pooled analysis of 25 clinical studies reported a dose-response cholesterol lowering effect independent of the type of nuts tested and similar across age groups and gender (29). Several other studies have now confirmed the cholesterol-lowering properties of nuts (23). Importantly, although the abundance of MUFAs in nuts is considered the main factor responsible for this action, it has also been reported that additional factors must contribute to the cholesterol-lowering activity, likely the presence of other bioactive phytochemicals, such as tocopherol, squalene, and phytosterol (30).

In recent years, evidence emerged on the protective effect of nuts against some chronic diseases, including metabolic syndrome (11) and type 2 diabetes (10,31,32). Nut consumption has also been shown to improve BMI and adiposity (12) and not to lead to weight gain (33,34). Accordingly, participants of the PREDIMED study and the NHS and HPFS studies who ate high amounts of nuts had lower BMI and less waist circumference (17–18).

**Nut Consumption and Cancer**

The first indications of a potential protective effect of nut consumption on cancer appeared already in the late 80s/early 90s. A case-control study of stomach cancer found a dose-response relationship for seven dietary items, including nuts (35). Similarly, a cohort study conducted on 14,000 Adventist men found a statistically significant reduction of prostate cancer risk associated with increasing consumption of beans, lentils, peas, tomatoes, raisins, dates, and other dried fruits (36). It must be noted, however, that only age-adjusted relative risks were statistically significant, whereas no statistically significant association was found in the multivariate models (36). The hypothesis that grains, cereals and nuts may be protective against prostate cancer was later supported by a study on prostate cancer in a Canadian population that discovered a 31% risk reduction (odds ratio [OR] = 0.69, 95% CI = 0.53 to 0.91), although in this study nuts were mixed with legumes and seeds (37). Evidence of a protective role of nuts on colorectal cancer in women also appeared with a prospective study conducted in Taiwan that recruited almost 24,000 people and followed them annually for 10 years (38). Beneficial effects of peanut consumption were observed in women, although the authors acknowledged some limitations of the study, including the lack of detailed information on other potential factors. Nevertheless, the European Prospective Investigation into Cancer and Nutrition (EPIC), which was one of the largest prospective cohort studies on diet and cancer, also showed a reduced incidence of colon cancer in women who had an average intake of 16 g of nuts and seeds daily, compared with nonconsumers (39). No observable effect was detected in men or on rectal cancer, although this might reflect the smaller number of rectal vs colon cancer case patients in the study and the fact that more women were recruited. In addition, according to a study conducted on Greek women, there appears to be a 27% reduced risk of endometrial cancer because of a diet rich in nuts, legumes, and seeds, although it has to be considered that this is a low-risk population for this type of cancer, and the study only had 84 cases of
women with confirmed endometrial cancer and 84 control patients (40). Taken together, these studies were all indicative of an inverse association between nut consumption and cancer.

The recent investigation of the association between nut consumption and total and cause-specific mortality assessed in the NHS and in HPFS (17) confirmed a statistically significant inverse association between nut consumption and deaths related to cancer in the pooled analysis of women and men (Table 1). Similarly, the recent longitudinal cohort study from the PREDIMED trial (18) also indicated that participants with a frequency of total nut consumption of more than three servings per week had a 40% reduction in cancer death (HR = 0.60, 95% CI = 0.37 to 0.98, \( P_{\text{trend}} \) not statistically significant [.064]). Interestingly, the hazard ratio in participants who specifically ate walnuts more than three servings per week was 0.46 (95% CI = 0.27 to 0.79, \( P_{\text{trend}} = .005 \)).

Taken together, these studies have provided some very strong support to the hypothesis of a beneficial effect of nut consumption on all cancer-related mortality. It must be noted, however, that these two studies analyzed the association between nut intake and cancer mortality. It would be important to establish now if the benefits are because of a reduction of cancer risk or survival or a combination of both. Furthermore, it would be interesting to assess whether nuts have stronger preventive effect on specific cancer types and possibly on specific subsets of certain cancer types. Some studies have already started to investigate this aspect. For instance, a prospective cohort study followed 75 690 women in the NHS and evaluated the association between nut consumption and pancreatic cancer risk (19). During a follow up from 1980 to 2010, the authors documented 466 cases of pancreatic cancer, and they identified an inverse association between frequent nut consumption and risk of pancreatic cancer. Specifically, women who consumed a 28-g serving size of nuts two times or more per week had an age-adjusted relative risk of pancreatic cancer of 0.65 (95% CI = 0.47 to 0.90; \( P_{\text{trend}} = .005 \)) and a multivariable relative risk of 0.65 (95% CI = 0.47 to 0.92; \( P_{\text{trend}} = .007 \)), compared with nonconsumers. Importantly, similar results were obtained after controlling for BMI and history of diabetes, for other dietary variables (such as alcohol consumption, multivitamin use, intakes of red meats, fruits, vegetables, and vitamin D) or after adjusting for the Mediterranean diet score. An inverse association also remained when the multivariate analyses were performed within subgroups of BMI, physical activity, smoking, and intakes of red meat, fruits, and vegetables or after adding a four-year lag period between nut intake assessment and each follow-up period, supporting the conclusion that frequent nut consumption was associated with reduced risk of pancreatic cancer (19). Recent results from a population-based case-control study involving 2865 case patients with 3299 control patients revealed an inverse association between nut consumption during adolescence and breast cancer risk in adult life (41). Specifically, adjusted odds ratios were 0.86 (95% CI = 0.71 to 1.04) for total nuts servings of one to three per month; 0.86 (95% CI = 0.72 to 1.04) for total nuts servings of one to six per week; 0.76 (95% CI = 0.61 to 0.95) for total nuts servings of one or more per day, compared with consumption of less than once per month (\( P_{\text{trend}} = .04 \)). The inverse association between total intake of nuts during adolescence and breast cancer risk was stronger for postmenopausal than for premenopausal breast cancer. These results were consistent with a previous study that analyzed the association between adolescent fiber and nuts intake and proliferative benign breast disease (BBD), a marker of increased breast cancer risk (42). This study showed that total nut intake of two or more servings per week during adolescence was inversely associated with proliferative BBD (multivariable HR = 0.64, 95% CI = 0.48 to 0.85, \( P_{\text{trend}} < .01 \)), compared with an intake of less than one serving per month. Statistically significant inverse association was also observed for peanuts intake alone.

Although some of these studies could not support a direct cause-effect association, they have definitely provided evidence of the beneficial effects of nut consumption and of their inverse association with cancer-related mortality. Questions remain on the cellular mechanisms responsible for their anticancer activity.

Mechanisms Involved in the Anticancer Properties of Nuts

Different hypotheses have been proposed to explain the protective effects of nuts, including the direct anticancer properties of several nut components, which can act in a synergistic way to block cancer cell proliferation. Furthermore, nuts contain many antioxidant and anti-inflammatory substances, and indeed some of the beneficial effects on cardiovascular diseases have been ascribed to the action of these components. With the growing evidence indicating the key role for inflammation and oxidative stress in the development of specific cancer types, it is very likely that the antioxidative and anti-inflammatory properties of some nut components also contribute to their anticancer activity. Finally, since reprogramming of energy metabolism has been recently recognized as a key feature of cancer cells, it can be hypothesized that nuts can affect cancer progression through their ability to alter lipid profiles and cell metabolism.

Anticancer Properties of Nut Phytochemicals

Over the last 20 years, epidemiological studies have indicated an inverse relationship between diet and development of cancer with a regular intake of fruits and vegetables clearly associated with a decreased risk of the disease. As a result, there has been a huge interest in studying the components responsible for this chemopreventive activity, which has led to the identification of several phytochemicals or bioactive compounds with different chemical structures and functions (43). Bioactive compounds or nutraceuticals are extranutritional constituents that typically occur in small quantities in food and are associated with beneficial effects on health (43). Nuts contain many bioactive compounds that have been found to affect several cellular processes involved in tumor development and progression, including cell survival, cell proliferation, cell invasion, and angiogenesis (43) and therefore can account for the anticancer properties of nuts. A few representative examples of some of these compounds, some of their anticancer activities and mechanisms of actions are listed in Table 2.

**Polyphenols.** Polyphenols are metabolites containing benzene rings with one or more attached hydroxyl groups, which include phenolic acids, flavonoids, stilbenes, and curcuminoids (44). In vitro and in vivo anticancer activity has been reported for some phenolic acids, such as anacardic acid, found in cashew shells
Biological effects

In vivo models

Molecular targets

Ellagic acid
(Walnuts and pecans)

Cell cycle arrest
Apoptosis

MDA-MB-231 breast cancer xenografts
(P52)

Inhibits: NF-κB pathway (50); COX2, cyclin D1, MMP-9, PDGF, VEGF expression

Anacardic acid
(Cashews shells)

Induces apoptosis and cell cycle arrest; inhibits cell growth, migration, invasion, angiogenesis and metastasis
Subrenal capsule xenografts

PC3 prostate cancer xenografts

Inhibits: NF-κB pathway (43); cyclinD1, COX2 and c-Myc expression (43,48); Bcl-2, Bcl-xL, c-FLIP, c-FLAP-1, survivin (43)

Genistein
(Hazelnuts, peanuts)

Induces apoptosis and cell cycle arrest; inhibits cell growth, migration, invasion, angiogenesis and metastasis

Subrenal capsule xenografts

Inhibits: NF-κB pathway (50,59); Akt, AP-1 (50); cyclinB1, VEGF and FGF-2 expression (43)

Resveratrol
(Peanuts)

Induces apoptosis, inhibits cell invasion, angiogenesis (43)

Several models of breast, colorectal, liver, pancreatic and prostate cancer (60)

Inhibits: NF-κB pathways (43,50); COX2, JNK, MEK, survivin, MMP-2/9, VEGF, FGF, IL-1, IL-6 expression (43) etc

Ins (1,3,4,5,6)P
(Cashews, peanuts)

Induction of apoptosis (69), inhibition of angiogenesis

SKOV3 ovarian cancer xenografts

Inhibits: PI3K/Akt pathway (68,69)

Table 2. Examples of phytochemicals present in nuts and their potential anticancer properties

Phytochemical and type of nuts

Biological effects

In vivo models

Molecular targets

(43,45–49) and ellagic acid, contained in walnuts and pecans (44,50–53). Similarly, genistein, a flavonoid mainly found in soybeans but also in nuts (54), has shown in vitro anti-invasive and in vivo antimitastatic activity (55–59). Within the group of stilbenes, resveratrol has been extensively studied for its anticancer properties, and it has been shown to be able to inhibit the three major stages of carcinogenesis: initiation, promotion, and progression, as well as tumor angiogenesis and cell invasion (60–64). Importantly, an inverse association was observed for resveratrol from grapes and risk of breast cancer (65). Interestingly, anacardic acid and resveratrol seem also to be able to counteract cancer-related epigenetic alterations (66).

Carotenoids. Carotenoids are naturally occurring fat-soluble pigments belonging to the group of tetraterpenes. Although they are present only in small amounts in nuts, it has been proposed that they can exert anticancer properties because of their antioxidant effect or, as in the case of lycopene, their direct effect on cancer cells (44).

Phytosterols. Phytosterols are chemically classified as 4-desmethylsterols, and they include β-sitosterol, campesterol, and stigmasterol, principally found in nuts, whole grains, seeds, and corresponding oils (44). β-sitosterol has been reported to possess antiproliferative and proapoptotic properties towards several cancer cells (44).

Phytoestrogens. Phytoestrogens are nonsteroidal compounds, structurally similar to estradiol (17-β-estradiol), which can act as estrogen’s antagonists. Accumulating evidence suggests that phytoestrogens may have protective action in some hormone-dependent diseases, including prostate, breast, and bowel cancer. It is worth noticing that some studies have found an inverse correlation between nut consumption and risk of colon and colorectal cancer, specifically in the female population (38,39), and therefore it is tempting to speculate that this could be, at least partially, because of the anti-estrogen activity of phytoestrogens.

Inositol Polyphosphates. A new interesting class of bioactive compounds is represented by inositol polyphosphates, the water-soluble head groups of phosphoinositides. Phytic acid or inositol(1,2,3,4,5,6)hexakisphosphate (InsP6), naturally found in legumes, wheat bran, soy foods, and nuts, possesses antitumor activity in vitro and in vivo (59). However, the very high concentrations required for InsP6 to be active (1–5 mM) suggest a lack of selectivity of this compound, although it is noteworthy that, even at these concentrations, inositol polyphosphates do not appear to have toxic effects (67). We reported the anticancer activity of the pentakisphosphate, Ins(1,3,4,5,6)P5, both in vitro and in vivo (68,69).

Diet Fiber. Fiber is one of the main components of all types of nuts. Although the role of a diet rich in fiber is yet to be clarified, evidence suggests a preventive action on cancer. A 21% risk reduction of colorectal cancer was observed among high fiber consumers in the EPIC study (70). A large case-control study on pancreatic cancer in Italy found an inverse correlation between soluble and insoluble fiber intake from fruit and risk of pancreatic cancer, and no association with grain fiber (71). Total, insoluble, and legume fiber intake was linked to a reduction of prostate cancer risk in a French prospective study, whereas no correlation was observed with soluble, vegetable, and fruit fiber intakes (72). In contrast, fruit fiber intake was inversely associated with prostate cancer risk in men participating in the EPIC study (73). Also in the EPIC study, a protective effect of vegetable fiber against breast cancer was found (74), which has been confirmed by the SU.VI.MAX study, but no correlation with fiber from other food sources emerged (75).

Vitamin and Micronutrients. Nuts are very rich in antioxidants such as tocopherols, magnesium, and selenium. The anticancer properties of vitamin E—a group of fat-soluble compounds that includes tocopherols—seem to be strictly related to their antioxidant properties (76). Magnesium plays a key role in many essential cellular processes, and its deficiency may be associated with inflammation. Magnesium homeostasis impairment is frequently

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observed in tumor cells (77). Selenium has been linked to many health benefits in humans, including decreasing the incidence of cancer (78).

**Potential Synergy of Nut Phytochemicals**

The use of bioactive compounds in cancer prevention and treatment has attracted increasing attention in recent years (79–81). Although extensively studied, the precise mechanism of action of most of them has not been completely elucidated yet. It is also important to underline that bioactive compounds are usually present in food at lower concentrations than those used in in vitro studies and reported to be effective. This observation may raise doubts about the effectiveness of a diet enriched in foods containing these compounds in cancer therapy. Some concerns also come from their actual bioavailability and bioactivity. In this respect, the possibility to enhance their activity by combining different compounds or, more importantly, by using specific foods that already contain a combination of these compounds, is very intriguing (16,82). It is worth mentioning that, although phytochemicals have been demonstrated to possess preventive effects on cardiovascular disease, cancer, and other chronic conditions (83–85), studies on single compounds have not reached the same positive results (86). This leads to the hypothesis that the protective effect could be because of a synergistic action of phytochemicals’ combinations normally found in these foods (16,82,87).

**Anti-inflammatory and Antioxidant Properties of Nuts in Cancer Prevention**

**Inflammation.** Inflammation has been associated with many of the cellular mechanisms involved in tumor progression, such as deregulated cell proliferation and survival, genome destabilization, and induction of migration and invasion (88). Inflammation has also been linked to genomic instability through several mechanisms, and it has been associated with all different steps that are involved in metastasis development (89). For instance, tumor-associated macrophages are critical for invasion and for intravasation of cancer cells into blood and lymphatics vessels, a process which is also facilitated by tumor necrosis factor–induced increase in vascular permeability, prostaglandin production, and matrix metalloproteinases–mediated tissue remodeling (90). Inflammatory mediators further enhance the survival of circulating cancer cells and promote their extravasation by inducing the upregulation of adhesion molecules.

Nuts possess several components with potential anti-inflammatory properties, including MUFA, magnesium, fiber, α-linolenic acid, and L-arginine (91–94). Quercetin and resveratrol also exhibit anti-inflammatory properties by acting on the formation of prostaglandins and proinflammatory cytokines involved in inflammatory response (95,96). Epidemiologic studies have suggested an inverse association between nut consumption and inflammation (91–94). In the PREDIMED study, a decrease in plasma concentrations of some inflammatory markers (IL–6, ICAM-1 and VCAM-1) was observed in the two interventional groups with Mediterranean diets compared with the control group after three months (97). Acute studies have also suggested a role for nut consumption in modulation of inflammatory response.

**Oxidative stress.** Oxidative stress has been observed in many cancers, both in solid tumors and hematopoietic malignancies. Evidence suggests that the accumulation of reactive oxygen species (ROS) could promote cell proliferation, cell survival, migration, and metastasis through several mechanisms. For instance, ROS can oxidize PUFA and activate lipid peroxidation, which in turn can alter membrane fluidity and increase membrane permeability, leading to leakage of intracellular enzymes and recruitment of inflammatory cells (98). In addition, lipid peroxidation can generate other free radicals and products that directly regulate gene expression and cell proliferation. ROS can also oxidize proteins, have been shown to induce oxidative modification to DNA bases, which can lead to mispair/mutagenic potential or affect DNA methylation, and are directly involved in the regulation of several cellular functions by activating key signaling pathways, including NF-κB, phosphoinositide 3-kinase (PI3K)/Akt, heat shock proteins, and mitogen-activated protein kinase (98). It is also important to note that some anticancer agents are able to induce cancer cell apoptosis by increasing ROS levels (99). Therefore, free radicals can play a dual role as both accelerator or inhibitor in carcinogenesis.

Nuts contain several antioxidant components, such as phytosterols, carotenoids, phenols (proanthocyanidins, flavonoids, resveratrol), and vitamin E (α-tocopherol, β-tocopherol and γ-tocopherol) (100–102). Selenium and magnesium are also key components of antioxidant enzymes (78,103). It has been suggested that a reduced susceptibility to low density lipoprotein (LDL) oxidation contributes to the protective effect of nut consumption on cardiovascular risk. A review of studies investigating the effect of nuts on oxidation concluded that, although results from animal studies and human clinical trials did not show consistent positive effects on oxidation status, there was no deleterious effect on oxidation (100). Therefore, the authors concluded that the antioxidant components may counteract the effect of the unsaturated fats (100). Among these components, resveratrol is one of the most studied for its anticancer activity. Interestingly, it has been shown that resveratrol can act both as oxidant and antioxidant, and it can reduce the expression of oncogenes.

**Nuts, Energy Metabolism, and Cancer**

Alteration of metabolic pathways is very common in cancer cells, and indeed reprogramming of metabolism has been recently recognized as an emerging hallmark of cancer (104). Although many studies have been focused on glucose metabolism and in particular on the ability of cancer cells to use aerobic glycolysis, there is currently an increasing interest in studying lipid metabolism and it is becoming overtly evident that the alteration of lipid metabolism is critical for cancer development (105). Several enzymes involved in lipogenesis and lipolysis have been found overexpressed in cancer, including fatty acid synthase that catalyzes the final steps during fatty acids synthesis (106), or monoacylglycerol lipase that releases free fatty acids from monoacylglycerols (107). Similarly, increased activity of the sterol regulatory element-binding protein (SREBP), or overexpression of its downstream targets, has been observed in several cancers (108). In addition, increasing evidence suggest that cholesterol plays a key role in cancer (109).

Consistent with the emerging role of lipid metabolism, the accumulation in specific lipid droplets (LDs) has been observed in
several cancers where they are thought to act as storage of triacylglycerols and cholesteryl ethers (CE) (110). A recent study has reported the specific role of these LDs in cancer cell proliferation, indicating their potential use as both biomarkers and molecular targets (111). Specifically, it has been shown that loss of the tumor suppressor phosphate and tensin homolog (PTEN) in prostate cancer and consequent activation of the PI3K/Akt pathway results in activation of SREBP and accumulation of CE in LDs. The mechanism of this accumulation involves uptake of LDL through an LDL receptor and the conversion of excess free cholesterol into CE by the action of the enzyme acyl coenzyme A:cholesterol acyltransferase (ACAT). In a normal cell, accumulation of free cholesterol would inhibit SREBP and LDL receptors, thereby reducing LDL uptake. Prostate cancer cells appear to use ACAT to remove the excess cholesterol and store it as CE into LDs in order to maintain uptake of LDL and associated fatty acids, including the key arachidonic acid that is involved in cell proliferation and growth.

One of the most accepted mechanisms responsible for the protective effect of nuts on cardiovascular diseases is their well-established lipid-lowering activity. A systematic review of studies published up to August 2004 reported that three studies on almonds, two studies on peanuts, one study on pecan nuts, and four studies on walnuts had consistently shown a decrease in total cholesterol (between 2% and 16%) and LDL cholesterol (between 2% and 19%) in people who ate nuts compared with people who ate control diets (112). A recent pooled analysis of 1284 observations by 583 participants from 25 clinical studies revealed a dose-response cholesterol-lowering effect, with a mean estimated reduction of total cholesterol and LDL-cholesterol of 5% and 7%, respectively, and no effect on HDL-cholesterol or triglycerides (except in subjects with serum triglycerides >150 mg/dL). The effect was dose related, similar by gender and across age groups and independent of the type of nuts tested. Importantly, the effect was greater for subjects with higher baseline values of LDL-cholesterol and those with lower baseline BMI (113). Similarly, a recent meta-analysis of 13 clinical trials showed that walnut-rich diets reduced LDL-cholesterol concentrations with no effect on HDL-cholesterol or triglycerides, compared with control diets (114). Recent intervention studies using walnuts, almonds, hazelnuts, pistachios, macadamias, and peanuts have all confirmed the LDL-cholesterol lowering effects (23). Interestingly, although this property has been mainly ascribed to the fact that nuts are rich in unsaturated fatty acids, it was also reported that the cholesterol-lowering effect was 25% higher than predicted on the basis of the nuts’ fatty acids profiles (23). Therefore, it has been suggested that other nut components, such as fibers, vitamins, folic acid, magnesium, copper, plant proteins and sterols, and phenolic components can also contribute to the cholesterol-lowering profile.

Since it is well documented that nuts have a cholesterol-lowering effect and they can modify lipid profiles in humans, it is tempting to speculate that some of their anticancer properties can be directly ascribable to their effect on lipid profiles. For instance, by lowering cholesterol levels they can reduce the accumulation of CE in cancer cells and therefore possibly reduce uptake of LDL and essential fatty acids, ultimately resulting in inhibition of cancer cell proliferation and tumor growth.

Despite the high fat content of nuts, their consumption has been shown to induce a decrease in body weight. In addition, nut consumption has also been shown to reduce visceral adiposity, hyperglycemia, insulin resistance, and endothelial dysfunction. These data suggest that nut consumption may affect cell metabolism. Since cancer cells have been shown to induce a specific metabolism reprogramming, it is tempting to hypothesize that nut effect on metabolism could counteract the cancer-specific cell metabolism.

**Pressing Questions**

Unwinding the tangle of nut consumption and cancer survival will require studies specifically designed to investigate this correlation. Throughout the review, we have attempted to provide some explanations for the protective role of nut consumption in cancer survival. Several questions still remain to be addressed.

1. Are there specific cancer types where nut consumption is more effective than others? Within a specific cancer type, are there specific subsets where nut consumption is more beneficial? Is there a potential association with specific mutations, signaling pathways alteration, etc.?
2. Are some nut species more effective than others?
3. Can nut consumption be used in combination with chemotherapy?
4. What are the best methodological approaches and animal models to study nut effects?
5. What are the amounts of nuts to be consumed to get a beneficial effect?

Future directions in order to get a stronger correlation between nut consumption and cancer chemoprevention involve epidemiologic research that narrows the focus on specific cancer types or types of nuts. It would be also interesting to perform studies in specific cancer settings and to investigate the association between nut consumption and cancer recurrence or metastasis in populations at high risk. Another key aspect to be investigated is the amount of nuts to be consumed and the potential interaction with other nutrients and demographic risk factors.

**Conclusion**

Since the publication of our review on cancer chemoprevention by nuts (16), research on the effects of nut consumption on cancer survival has substantially increased the evidence of an inverse correlation. In this review, we have focused our attention on the potential mechanisms responsible for the chemopreventive properties of nuts. This is a very interesting topic that further requires future investigation specifically designed to address this question. Population-based studies on the association between nuts and cancer have often been limited by the fact that they grouped nuts, legumes, and seeds, they measured dietary intake at baseline, or had insufficient statistical power because of limited cancer cases and distribution of nut intake. Therefore, better epidemiological studies, in particular large prospective cohort studies to assess the association between nut consumption and cancer, are urgently needed. The compelling evidence that increased nut consumption is associated with statistically significant reduction
of mortality risk, including cancer, suggest that nut consumption should be considered a tool of intervention to reduce the burden of cancer. More importantly, this reinforces the rationale that nuts should be included as a serving in the fruit and vegetables serving recommendation.

References


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