Received: 2 January 2023 | Accepted: 6 July 2023

DOI: 10.1002/cdt3.87

Chronic Diseases and Translational Medicine

REVIEW

Nut consumption and urogenital and genital, gastrointestinal and women-related cancers: Assessment and review

Maryam Mohamadi[1] | **Periklis Dousdampanis**[2] | **Zahra Ahmadi**[3] | **Soheila Pourmasumi**[4,5] | **Monavare Naderi**[6] | **Nahid Zainodini**[7] | **Alireza Nazari**[8]

[1]Occupational Safety and Health Research Center, NICICO, World safety organization and Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[2]Department of Nephrology, Saint Andrews State General Hospital, Patras, Greece

[3]Pistachio Safety Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[4]Social Determinants of Health Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[5]Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[6]Vice Chancellor for Research and Technology, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[7]Immunology of Infectious Diseases Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[8]Department of Surgery, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Correspondence

Alireza Nazari, Department of Surgery, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
Email: drnazari57@gmail.com

Edited by Yi Cui

Abstract

The prevalence of cancer, especially in industrial countries, is a major problem for health and treatment systems. Cancer can affect the quality of life of all family members and has many negative effects on the community. Despite many advances in cancer treatment, this disease is still a major worldwide problem. There is strong evidence that dietary habits are effective in protecting against cancer and even helping in the disease treatment progress. Nuts with various biologically-active compounds, such as vitamins, phytosterols, isoflavones, flavonoids, and polyphenols have been reported to possess anticarcinogenic properties. Accordingly, this review provides an insight into the association between nut consumption and the prevention of some cancers. We considered the cancers related to the urogenital and genital tract, gastrointestinal tract, as well as women-related cancers. Both cell culture examinations and experimental animal studies alongside observational epidemiological studies demonstrated that regular consumption of a nut-enriched diet is able to reduce the risk of these cancers.

KEYWORDS

bladder, breast, cervical, nut, prostate

Key points

- Nuts can potentially inhibit the development and progression of some cancer types.
- Nuts contain biologically active compounds with anticarcinogenic properties such as folate, phytosterols, saponins, phytic acid, isoflavones, ellagic acid, α-tocopherol, quercetin, and resveratrol.
- Evidence suggests that consuming nuts may reduce the risk of cancer and cancer-related mortality.
- These findings support dietary recommendations to increase nut consumption to reduce cancer-related risk and mortality.

1 | INTRODUCTION

1.1 | Cancer and nut consumption

Cancer occurs when an organism genetically loses control of the growth and proliferation of the cells.[1] Approximately 90.5 million people were suffering from cancer in 2015[2] and it was estimated that around 14.1 million (excluding skin cancers) new cases would be added each year.[2] In 2015, cancer deaths were 8.8 million, accounting for 15.7% deaths.[3] The most frequent types of cancer were lung, prostate, colorectal, and stomach cancers in men and breast, colorectal, cervical, and lung cancers in women.[2] About 90%–95% of cancer cases, are etiologically a result of genetic mutations raised by lifestyle and environmental factors.[4]

Extensive scientific-based evidence from both cell culture examinations and experimental animal studies alongside observational epidemiological studies have demonstrated that regular consumption of a nut-enriched diet is able to reduce the risk of several chronic diseases, including cancer.[5–9]

The term "tree nuts" refers botanically to a type of dry fruit which usually contains one seed (and rarely two seeds) within the ovary wall that hardens when it is ripen. These nuts are almonds, walnuts, pistachios, hazelnuts, cashews, as well as pecans.[10] In contrast to the tree nuts, peanuts, and Brazil nuts are, respectively, classified into legumes and seeds. However, they are designated as nuts, due to exhibiting similar nutritional benefits and properties of the tree nuts.

Many reports have evidenced that high consumption of nuts is associated with a reduced risk of cancer.[11–13] For example, an investigation claimed that the event of death due to various types of cancer had an inverse relation with the consumption of nuts.[11] In another study, the participants who had consumed 10 g/day or more of nuts, demonstrated a reduced rate (21%) of mortality from cancer in comparison to nonconsumers.[14] Aune and colleagues have stated that the intake of approximately 15–20 g/day of nuts is associated with a reduction of 18% in total cancer risk.[15]

The results of a cohort study also indicated that intake of nuts >3 servings/week was considerably related to reduced cancer mortality (one serving: 28 g of nuts, nuts: almonds, peanuts, hazelnuts, pine nuts, walnuts, pistachios, macadamia, Brazil nuts, and cashews).[16] Walnuts were more effectively correlated with the reduced risk of cancer mortality in comparison to all other kinds of nuts.[16] According to the results of a meta-analysis article in 2022, an increase in nut consumption by 10 g/day is related to a reduction of overall cancer mortality by 20%.[17]

In addition, the findings of another study indicated that regular consumption of walnuts is beneficial for various diseases, including cancer.[18] Jahanbani et al. reported that a bio-peptide which was derived from walnut residual proteins showed remarkable anticancer potential against human colon (HT-29) and breast (MDA-MB231) cancer cell lines.[19] Intake of walnuts and peanuts has been found to reduce the risk of cancer development because they have anticarcinogenic components.[20] A substudy of the Walnuts and Healthy Aging trial showed that supplementation with 30–60 g/day of walnuts for 1 year resulted in the upregulation of hsa-miR-551a, a circulating microRNA which is related to reduced cell migration and invasion in several carcinomas.[21]

The anticancer properties of pistachios have also been reported.[22] Previous studies have also revealed the anticancer and antiangiogenesis[23] effects of pistachio (*Pistacia vera* L.) components such as hull, leaves, seed, essential oil, and gum.[24]

1.2 | Anticancer phytochemicals of nuts and possible mechanisms

Nuts are well known as the main source of several nutrients, like folate, phytosterols, saponins, phytic acid, isoflavones, inositol hexaphosphate, and resveratrol which possess anticarcinogenic properties.[25,26] Table 1 summarizes some anticancer phytochemicals of nuts with related mechanisms.

Although the exact mechanism of the cancer-protective effects of nuts is not clear, their main beneficial impact is ascribed to their anti-inflammatory and antioxidant compounds. Antioxidants in nuts, such as vitamins A, B, and E, melatonin, zinc, magnesium, phytosterols, omega-3 polyunsaturated fatty acids, and several polyphenols, can prevent oxidative stress and protect DNA from being damaged by reactive oxygen species.[29] Phenolic compounds have been demonstrated to have protective effects against diseases in which overproduction of free radicals is occurred, including various types of cancer.[30,31] Quercetin and resveratrol which are abundant in pine nuts, are the most well-known compounds of this group.[32] These polyphenols can influence the formation and metabolism of prostaglandins and proinflammatory cytokines involved in carcinogenesis.[33–35] Furthermore, quercetin and resveratrol are able to inhibit chemically induced carcinogenesis.[9]

Ellagic acid is a polyphenol mostly found in walnuts and pecans[36] is able to attenuate chemically-induced carcinogenesis, as well as prevent proliferation and initiate the apoptosis of cancerous cells.[32] It has been revealed that nuts which contain ellagic acid exerted anticancer activity in various tumor models.[37,38]

Juglanin is a flavonoid found in walnut and, like other members of this family, exerts inhibitory activity against growth of several cancers, including breast, lung,[39] and skin.[40,41]

Peanuts are also known as a rich source of isoflavones, phytosterols, resveratrol, and phenolic acid,[42,43] all of which possess anticancer properties.

TABLE 1 Selected phytochemicals in nuts associated with cancer prevention.[1,27,28]

Class	Compound	Source	Mechanism
Flavonoids	Resveratrol	Pine nuts, peanuts	Induction of the enzymes involved in phase-2 metabolism
	Quercetin	Pine nuts	Regulation of inflammatory response and immunological activity
Vitamins	Folic acid	Almonds, pine nuts, hazelnuts	Reduction of DNA damage
	Vitamin E	Hazelnuts, almonds, pine nuts	Acting as antioxidant, modulation of gene expression, inhibition of cell proliferation, and adhesion
Polyphenols	Ellagic acid	Almonds, pine nuts, walnuts, pecans	Inhibition of chemically induced carcinogenesis
Isoflavonoids	Lignans, deidzein, genistein	Brazil nuts, hazelnuts	Regulation of hormonal mechanisms
Fatty acids	Oleic acid	Hazelnuts, macadamia	Supply of monounsaturated fatty acids
Others	Dietary fiber	Almonds, walnuts, pistachio	Supply of dietary fiber
	Selenium	Almonds, hazelnuts, Brazil nuts, walnuts, cashew nuts, pecans	Antioxidant

Carotenoids as one of the constituents of nuts have antioxidant properties which are related to the reduced risk of some types of cancer.[44] Vitamin E, which is also present in nuts, is one of the natural antioxidant compounds. Although selenium itself is not known for its antioxidant nutritional properties, it serves as a component of antioxidant enzymes.[45] This element is found in the Brazil nut, cashew, walnuts, and pecans.[46] Pistachios also have considerable levels of selenium, as well as zinc; both of them are known for the prevention of some types of cancer.[47]

Arginine has proposed to be able to exert its protective effects against cancer[48,49]; almond contains some types of proteins that are enriched in high levels of arginine.

Folate has been suggested to play a role in cancer prevention due to its integral role in the synthesis and methylation of DNA.[50,51] Folate deficiency may cause chromosomal rupture and its subsequent genetic instability. Chromosomal ruptures have the ability to be repaired, nonetheless, whenever the fragility of chromosomes is increased; the risk of cancer is also increased.[52,53] The good news is that nuts are a source of folic acid.[1]

Nuts are also considered as rich sources of fiber that has beneficial effects on gastrointestinal system, and accordingly is able to potentially lessen the risk of the occurrence of cancer in this system.[1] Nuts are also described as rich reservoirs of monounsaturated fatty acids (MUFA) and high consumption of MUFA alongside with the elevated MUFA/SFA (saturated fatty acids), ratio is well evidenced to be related to the reduction of the risk of cancer, particularly colorectal, prostate and breast cancers (BrC).[1] These compounds have been demonstrated to decrease tumor initiation and promotion.[18,54]

The aim of this review paper was to aggregate the main references and data to determine the association of nut consumption and risk of some urogenital and genital, gastrointestinal, and women-related cancers.

2 | METHODS

To collect the most useful and the best-related information concerning the association of nut consumption and cancer risk, we have searched the below keywords within online scientific databases including "Web of Sciences," "PubMed," "Science Direct," and "Scopus": nut, cervical cancer (CeC), BrC, colorectal cancer (CRC), colon cancer (CC), pancreas cancer (PC), bladder cancer (BC), and prostate cancer (PCa). On the basis of a review of titles and abstracts, the most-related ones were selected for writing the present review article.

3 | RESULTS

Table 2 shows a summary on the results of the studies reviewed here and is described in detail below.

3.1 | Urogenital and genital tract cancers

3.1.1 | Prostate cancer

PCa regarded as male cancer, has been considered the second most prevalent cancer in men; more than 1.2 million diagnosed cases of PCa was reported in 2018, worldwide.[75]

Unfortunately, investigations into nut intake and PCa incidence are limited and have emerged with discrepant reports. The Netherlands Cohort Study (2019) on 58,279 men aged 55–69 years exhibited no remarkable correlation between the consumption of peanuts, other tree

TABLE 2 Association of nut consumption and the risk of different cancers (Based on the results of the studies reviewed in the present article).

Cancer	Sample of the study	Effect on the cancer	References
Prostate cancer	The Netherlands Cohort Study	No remarkable association	[29]
	In vitro	Inhibition of the proliferation of PCa cells	[43]
	Cross-national study	Inverse association	[55]
	Population-based studies in Canada	Remarkable inverse association	[56]
	The Health Professionals Follow-up Study	No significant association	[57]
	Ecological study including 170 countries	Inverse association	[58]
	Greek population	No significant association	[59]
Bladder cancer	Patients newly diagnosed with bladder cancer	Inverse association	[60]
	Three large prospective cohort studies	No significant association	[61]
Pancreas cancer	The Nurses' Health Study	Inverse association	[11]
	The Netherlands Cohort Study	A nonlinear dose–response relation	[62]
	Population-based case-control study in the Netherlands	No significant association	[63]
Colon cancer	In vitro	Inhibition of the survival of colon cancer cells	[19]
	In vivo study on mice model	Inhibition of nuclear factor kappa β signaling in intestinal epithelial cells	[64]
	In vitro	Significant decrease in the growth of colon cancer cells	[65]
	In vivo study on mice model	Suppression of colon carcinogenesis	
Colorectal cancer	In vivo study on mice model	Significant inhibition of the development of colorectal cancer	[66]
	Tai population	Inverse association	[67]
	The Netherlands Cohort Study	Nonlinear inverse association	[68]
Breast cancer	South-African women with breast cancer	Inverse association	[69]
	97 patients and 104 control subjects	Inhibition of breast cancer development	[70]
	Population-based case-control study in Iran	Inverse association	[71]
	Prospective cohort study in the United States	Inverse association	[72]
Cervical cancer	A cross-sectional study in Shanxi	Inverse association	[73]
	In vitro	Decrease in the growth of cervical cancer cells	[74]

Abbreviation: PCa, prostate cancer.

nuts, and total nuts and advanced, nonadvanced, and total PCa. However, consumption of peanut butter was observed to have a direct relationship with the risk of nonadvanced PCa.[29]

Peanuts and walnuts have been also considered as the most prominent sources of phytosterols that inhibit proliferation of PCa cells in vitro.[43] Findings of a cross-national study on PCa mortality (i.e., PCa deaths per 100,000 males aged 45–74 years old) between 1985 and 1989 in 59 countries have exhibited a negative correlation between PCa-related mortality and the calories supplied from nuts and seed oils.[55]

Population-based studies performed in Canada[56] to make an adequate expectation for dietary intake using a dietary history reported a remarkable attenuation (31%) in the risk of PCa. However, this finding was true for total nuts, seeds and legumes, and their individual effects were not differentiated.

Wang and co-workers claimed that a significant correlation was not observed between the consumption of nuts and PCa incidence or its related mortality. Overall mortality was remarkably reduced (34%) when nuts were frequently consumed (five or more times per week) after PCa diagnosis. They confirmed PCa diagnosis with medical records and pathology reports. Deaths were also identified using family reports and National Death Index searches.[57]

The dietary supplementation with α-tocopherol has been reported to be markedly associated with the reduced incidence of PCa. In other words, higher levels

of serum α-tocopherol was well associated with a decreased risk of PCa.[76,77]

A recent ecological study including 170 countries, that assessed the link between dietary factors and PCa, demonstrated inverse associations between the consumption of seeds and nuts and the incidence (β −0.7, $p < 0.001$), prevalence (β −2.1, $p < 0.001$), and mortality (β −0.1, $p = 0.02$) rates of PCa.[58]

Vaioulis et al. studied the possible effects of the Mediterranean diet on PCa in a Greek population consisting of 279 healthy men and 431 patients suffering from PCa. The patient group was selected after prostate biopsy of the participants who had a PSA level ≥4 ng/mL or a positive digital examination, or a lesion suspicious for malignancy in the transanal ultrasound examination. Although they did not find a significant association between the dietary patterns and the incidence of PCa, daily intake of nuts (odds ratio [OR]: 0.63), white meat (OR: 0.59), whole grains (OR: 0.55), and dairy products (OR: 0.64) was higher in the healthy group. In addition, consumption of nuts with a frequency of less than once a week was correlated with the increased prevalence of PCa (OR: 1.8).[59]

Different studies on the association of PCa and nut consumption show inconsistent results, either a non-significant or a protective association. However, several epidemiological studies have demonstrated that metabolic syndrome might increase PCa risk and reduce survival.[78–80] Accordingly, consumption of a nut-supplemented diet aiming a healthy body mass index, might improve quality of life and consequently, increase survival.[81]

Regarding the mechanism of the possible association of nut consumption and PCa cancer, it can be attributed to the hormone-mediated nature of this cancer.[55] It has been reported that phytoestrogens, especially isoflavonoids and lignans, as well as other polyphenols, phytosterols, and even some fatty acids, which are abundant in nuts modify hormonal mechanisms or conduct antiestrogenic activity. Hence, these compounds of nuts may contribute to the prevention of hormone-dependent cancers.[33,34,82–84] Moreover, omega-3 fatty acids have shown inhibitory effects on the growth of tumors in prostate.[85,86]

3.1.2 | Bladder cancer

Nuts are a good source of vitamin E. Vitamin E has exhibited intracellular antioxidant properties.[87] α-Tocopherol, as the most abundant and active form of vitamin E in humans, is also able to enhance immune response, in addition to the modulation of gene expression, and inhibition of cell proliferation, and adhesion.[88]

Wang and colleagues performed a meta-analysis on 20 observational studies alongside the reported data from 7693 BC cases and suggested that intake of vitamin E was remarkably associated with the decreased risk of BC.[89] Lin et al. also demonstrated an inverse association between the intake of vitamin E and BC risk.[90]

Several in vitro studies have confirmed that ellagic acid which is contained in nuts has antiproliferative and cytotoxic effects on BC cell lines.[91–93] Ellagic acid can improve the antitumor property of mitomycin C in several types of human BC cell lines. Claudia and colleagues observed that ellagic acid found in nuts causes a considerable reduction in the proliferation rate, infiltrative behavior, and tumor-associated angiogenesis of human BC xenografts. Accordingly, they proposed this polyphenol for the adjunct therapy of BC.[94]

In a work study on 113 patients with BC and control sample ($n = 292$), the association between nut consumption and BC was investigated. It was found that intake of nuts was related with the reduced BC risk by 76% (OR, 0.24; 95% confidence interval [CI], 0.12–0.48).[60]

However, the results of another study on the data of the Health Professionals Follow-up Study (1986–2018), the Nurses' Health Study (1980–2014), and the Nurses' Health Study II (1991–2015) showed that frequent nut consumption had no significant relation with the risk of BC.[61]

3.2 | Gastrointestinal cancers

3.2.1 | Pancreas cancer

PC is regarded as the fourth leading cause of death associated with cancer, worldwide. Also, it has been evidenced that the PC incidence in developed countries is continuously elevating.[95]

It has been demonstrated that elevated levels of baseline plasma insulin and C-peptide are significantly correlated with the increased risk of subsequent PC.[62] Unsaturated fatty acids, magnesium, and fiber from nuts have been reported to be able to improve insulin sensitivity.[96]

Bao et al. investigated the association between nut consumption and the risk of PC with prospective following 75,680 women in the Nurses' Health Study. After adjusting for relevant variables, they found that the participants who consumed a nut serving size of 28 g twice or more per week, experienced a considerably lower risk of PC (RR, 0.65; 95% CI, 0.47–0.92; P for trend = 0.007) in comparison to nonconsumers.[11]

In the follow-up phase (20.3 years) of the Netherlands Cohort Study (with 120,852 participants), 583 incident PC cases, including 349 microscopically confirmed PC (MCPC) cases were reported. Multivariable case–cohort analyses of these PC cases by Nieuwenhuis and van den Brandt in 2018 showed a nonlinear dose–response relation between the intake of tree nuts and the incidence of MCPC. Consumption of peanut

butter was also associated to a significantly decreased risk of MCPC in men while unclear relation was found in women.[97] In a meta-analysis study in 2020, subgroup analyses of the association between specific types of cancer and nut consumption revealed an inverse association for PC.[98]

Zhao and co-workers reported that ellagic acid had the capability to exert in vivo therapeutic effects against PC.[63] Ellagic acid has also been demonstrated to inhibit nuclear factor kappa B in PC cells and induce apoptosis.[99]

However, a population-based case-control study conducted in the Netherlands in 1991 showed no positive relationship between PC and nuts intake.[100]

3.2.2 | Colon cancer

CC is one of the most prevalent solid tumors and is considered as a primary cause of cancer-related mortality, worldwide.[101] In most cases, CC achieves a better prognosis if immediately diagnosed at the initiation phase, and in this case, the 5-year overall survival rate of the patient can be up to 80%–90%.[102] Some population-based studies have proposed that 90% of mortality caused by large bowel cancer are due to the high intake of saturated fat and red meat which elevate the risk of CC.[103,104]

A study on the mice model of CC indicated that walnut consumption suppressed colon carcinogenesis.[105]

The inhibitory effects of phytosterols, phytic acid, and resveratrol on CC have been well supported by both in vitro and in vivo studies.[64,106] Peanut is a well-known source of phytosterols,[43] phytic acid,[43] and resveratrol.[65] β-Sitosterol, as the main component accounting for approximately 80%,[43] possesses protective effects against CC and inhibits the proliferation of HT-29 CC cells.[107]

A peptide fraction which was gained by the chymotrypsin-based hydrolysis of walnut protein has been reported to inhibit the survival of HT-29 and MDA-MB231 CC cells. This inhibitory effect was attributed to the antioxidant activity of the hydrolysate.[19]

Koh and co-workers conducted an in vivo study on mice model of CC and found that the phenolic extract of walnut was able to ameliorate colitis-associated CC via inhibiting nuclear factor kappa B signaling in intestinal epithelial cells.[108]

To study the metabolites formed during the fermentation of nuts in the human digestion system, Lux et al. prepared fermentation supernatants from the dietary fiber of macadamias, almonds, hazelnuts, walnuts, and pistachios and investigated their effects on the growth of HT29 cell line. They observed that all of the prepared fermentation supernatants, except that of pistachio, significantly decreased the growth of HT29 cells.[109]

3.2.3 | Colorectal cancer

Etiological evidence indicated that over 85% cases of CRC are well-correlated with environmental factors,[110] in particular dietary factors.[111]

In men and women, CRC has been reported to be the third and second most frequent cancer types, respectively.[112] Despite several well-defined risk factors such as age, familial history, and genetic inherited defects, CRC prevalence has been found to be higher in subjects suffering from obesity,[113,114] metabolic dysregulation,[115] insulin resistance,[116] and/or type-2 diabetes mellitus.[117–121] Cirillo et al. have reported 13 miRNAs as potential molecular links between metabolic alterations related to obesity and CRC onset and development.[114] According to the hyperinsulinemia hypothesis, elevated levels of insulin and free IGF-1 lead to the promoted proliferation of colon cells and survival of transformed cells, which ultimately result in CRC.[118] Since the consumption of nuts can remarkably improve insulin resistance,[66] lower weight gain,[122] and decrease the risk of type-2 diabetes mellitus,[123] intake of nuts may also attenuate the risk of developing CRC.

Findings of a research by *Nagel* et al. showed that walnut intake significantly inhibited the development of CRC in a mice model via suppressing angiogenesis.[67]

Additionally, some epidemiological studies have linked the intake of methionine and folate, which are found in abundance in nuts, to a decreased risk of CRC and colorectal adenomas. The possible corresponding mechanism, especially the effects of genetic polymorphisms, has been also investigated.[27,124]

Yeh's research group performed a study on 11,917 women and 12,026 men aging 30–65 years in Tai population and demonstrated that regular intake of either peanut or its products was able to reduce CRC risk in women, due to its antiproliferative effects.[68]

Wu and co-workers surveyed 30,708 participants in a meta-analysis review and reported a significant association between the consumption of nuts and reduced risk of CRC.[125]

Recently, another meta-analysis of observational studies on the effects of phytochemically rich diets and CRC risk has confirmed the finding of Wu et al. Borgas and co-workers reported a significant association between higher consumption of dietary nuts and decreased risk of CRC.[126] However, they observed a significant heterogeneity that made it difficult to achieve a reliable conclusion based on currently available data.

Analyzing the data of the Netherlands Cohort Study (with 120,852 participants), Nieuwenhuis and co-workers found nonlinear associations between the consumption of nuts and peanut butter and decreased risk of rectal cancer in women. However, borderline significant nonlinear relations were observed for men who consumed nuts. Surprisingly, the intake of peanut butter was observed to be related to a raised risk of CRC

that did not progress via the serrated neoplasia pathway in men.[127]

3.3 | Cancer-related to women

3.3.1 | Breast cancer

BrC is known as the main cause of cancer deaths in women, globally. Different risk factors have been identified for BrC, including age, breast density, reproductive history, lactation, genetic factors, hormone levels or use, lifestyle-related factors, and diet.[69,128,129] While some of these factors are not modifiable, dietary patterns and lifestyles can be modified to prevent BrC development.[70,71]

Consumption of nuts, including peanuts, walnuts, and almonds have been reported to decrease the risk of BrC by two to three folds.[20,43] Also, Bao et al. reported similar effects of nut consumption on the development of BrC.[11] Jacobs et al. investigated the effects of the consumption of nuts and seeds on 396 South-African women with BrC and found that the stratification of estrogen receptor-positive was inversely associated with the risk of the disease.[72]

In another study on 97 patients with BrC and 104 healthy control women, protective effects of peanuts, almonds, and walnuts for the inhibition of BrC development was observed.[130]

The results of a population-based case-control study on 350 Iranian women with pathologically confirmed BrC showed an inverse association between the intake of nuts (walnut, almond, hazelnut, and peanut) and the odds of BrC.[131]

Berkey and co-workers studied the combined effects of adolescent alcohol use and nut consumption on the risk of benign breast disease in young women, using the data of a prospective cohort study on 9031 females aged between 9 and 15 years (at baseline). As a main result, it was found that nut consumption mitigated the risk of the disease in high-school females, who drank.[132]

Ellagic acid, which exists in nuts, has been demonstrated to exert therapeutic effects against BrC in an in vivo study.[133] Peanuts are a well-known source of phytosterols, especially β-sitosterol, which have a protective role against BrC, as shown in an in vitro study.[43]

However, two investigations revealed no positive correlation between BrC and the intake of nuts.[100,134]

3.3.2 | Cervical cancer

CeC, which is potentially preventable,[135] is the second most frequent cancer type in women, worldwide.[136] In developing countries, CeC is considered the most frequent female genital tract malignancy.[137,138] Approximately 500,000 newly diagnosed cases and 273,000 deaths due to CeC are reported per year. Eighty-five percent of these deaths are occurred in developing countries.[136]

Nuts may be good anticancer candidates for CeC because they contain numerous substances with potential anticarcinogenic activity. A cross-sectional study in Shanxi, China showed an association between the dietary intake of nuts and the reduced risk of cervical intraepithelial neoplasia grade 2 or higher while controlling for human papillomavirus infection.[73]

Burin and co-workers investigated the effects of the oil of pecan nut on cervical squamous cancer cells (SiHa) using MTT assay and reported IC_{50} of 16.46 μg/mL and selectivity index of 0.75.[74]

In addition, different constituents of nuts have been demonstrated to be effective against CeC. In a study on 20,000 women aged <65 years in Yangqu County, a significant association between low levels of serum folate and the risk of cervical intraepithelial neoplasia progression was observed.[139]

Phenolics, quercetin, and resveratrol are compounds that regulate immunological activity and inflammatory response. These compounds have been reported to be remarkably involved in prostaglandins and proinflammatory cytokines generation that further intervene with inflammatory responses.[32,36] This mechanism might be paramount important in tumors displaying a pattern of chronic inflammation, including CeC.[32]

Juglone which is found in different parts of plants in the Juglandaceae family particularly the black walnut, has interesting anticancer effects against human CeC.[39,140–142] For instance, Lu and colleagues studied the possible regulatory effects of juglone on the apoptosis of CeC cells, and the related molecular mechanism. They observed that Juglone induced the expression of apoptotic molecules in mitochondrial and death receptor pathways via JNK/c-Jun activation pathway and further apoptosis of the CeC cells.[39]

In addition, Zhang and his research team reported that treatment of Hela cells with juglone resulted in some typical morphological changes in apoptotic body formation. The early apoptotic Hela cells detected using Annexin V-FITC were 5.23%, 7.95%, 10.69%, and 20.92% in response to 12.5, 25, 50, and 100 μmol/L of juglone, respectively. Bcl-2 expression was significantly downregulated while Bax expression was remarkably upregulated, in response to various concentrations of juglone after 24-h treatment. These events were alongside with the activation of caspases-3, -8, and -9, as well as PARP (polymerase) cleavage. According to these findings Zhang et al. proposed juglone as a good candidate for the treatment of HeLa cells.[140]

In another study, Zhang and colleagues surveyed the effects of juglone on the proliferation of SiHa cells. They demonstrated that Juglone was able to significantly induce the apoptosis of the cells and remarkably inhibit their proliferation.[141]

Zhang and co-workers also studied the effects of Juglone on human CeC Caski cells and reported that Juglone considerably prevented the proliferation of the cells and simultaneously elevated apoptosis in the Caski cells.[142]

4 | CONCLUSION

In an overall view, this should take into account that nuts are potentially able to inhibit the development and progression of some cancer types. Nuts contain various biologically active compounds, such as folate, phytosterols, saponins, phytic acid, isoflavones, ellagic acid, α-tocopherol, quercetin, and resveratrol which possess anticarcinogenic properties. This review provides relative evidence that consumption of nuts may attenuate the risk of cancer, and/or decrease cancer-related mortality. These findings support dietary recommendations to increase nut consumption to reduce cancer-related risk and mortality.

AUTHOR CONTRIBUTIONS

Maryam Mohamadi: Substantial contributions to conception and design; or acquisition, analysis, or interpretation of data. **Zahra Ahmadi**: Drafting of the article or critical revision for important intellectual content. **Soheila Pourmasumi**: Drafting of the article or critical revision for important intellectual content. **Monavare Naderi**: Drafting of the article or critical revision for important intellectual content. **Nahid Zainodini**: Drafting of the article or critical revision for important intellectual content. **Alireza Nazari**: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. Final approval of the version to be published. All authors have reviewed and approved the final manuscript.

ACKNOWLEDGMENTS

The authors appreciate the support of this work by Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

None.

ORCID

Alireza Nazari http://orcid.org/0000-0001-8352-793X

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How to cite this article: Mohamadi M, Dousdampanis P, Ahmadi Z, et al. Nut consumption and urogenital and genital, gastrointestinal and women-related cancers: Assessment and review. *Chronic Dis Transl Med*. 2023;9:277-287. doi:10.1002/cdt3.87