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# Nut Consumption and Risk of Cancer: A Meta-analysis of Prospective Studies

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## ABSTRACT

**Background:** Epidemiologic studies have investigated the association between nut intake and risk for multiple cancers. However, current findings are inconsistent and no definite conclusion has been drawn from prospective studies. We therefore conducted this meta-analysis to evaluate the relationship between nut consumption and risk of cancer.

**Methods:** Prospective studies reporting associations between nut intake and risk for all types of cancer were identified by searching Web of Science and PubMed databases up to June 2019. Risk ratios (RR) and 95% confidence intervals (CI) were extracted and then pooled across the studies using a random-effect model. A dose–response analysis was modeled by performing restricted cubic splines when data were available.

**Results:** Thirty-three studies that included more than 50,000 cancer cases were eligible for the analysis. When comparing the highest with the lowest category of nut intake, high consumption of nuts was significantly associated with decreased risk of overall cancer (RR = 0.90; 95% CI, 0.85–0.95). The protective effect of nut consumption was especially apparent against cancers from the digestive system (RR = 0.83; 95% CI, 0.77–0.89). Among different nut classes, significant association was only obtained for intake of tree nuts. We also observed a linear dose–response relationship between nut consumption and cancer: Per 20 g/day increase in nut consumption was related to a 10% (RR = 0.90; 95% CI, 0.82–0.99) decrease in cancer risk.

**Conclusions:** Our analysis demonstrated an inverse association of dietary nut consumption with cancer risk, especially for cancers from the digestive system.

**Impact:** This study highlights the protective effect of nuts against cancer.


## Introduction

Cancer is a major cause of death and constitutes a huge public health hazard worldwide. With rapid growth and aging of population, the global burden of cancer is expected to 29.5 million new cancer cases and 16.4 million cancer-related deaths by 2040 (1). According to recent evidence, approximately 40% of cancer can be prevented by avoiding potential modifiable risk factors such as tobacco use, alcohol consumption, unhealthy diet, lack of exercise, and infectious agents (2). In particular, the adherence to a healthy diet like Mediterranean dietary pattern has been proved to reduce the risk of some cancers by 4% to 57% (3).

As a part of healthy dietary pattern, nuts contain a wide range of nutrients with recognized benefits to human health including monounsaturated or polyunsaturated fatty acids, diet fiber, vegetable proteins, vitamins (tocopherol and folic acid), minerals (calcium, magnesium, potassium, and selenium), phytosterols, and polyphenols (4). Extensive evidence suggested that nut intake may have beneficial impact on long-term health by reducing intermediate mediators of chronic diseases such as insulin resistance, inflammation, hyperglycemia, and oxidative stress (5). On the basis of *in vitro* and *in vivo* studies, numerous components in nuts were likely to affect various biological behaviors of tumors. Preclinical evidence from *in vitro* models demonstrated that several nut compounds (resveratrol, ellagic acid, anacardic acid, omega 3 and 9 fatty acids) could induce cancer cell death, inhibit the proliferative capacity of cancer cells, and reduce their metastases to distant sites via the inhibition of critical cancer molecular pathways, such as NF-κB, matrix metalloproteinases, and VEGF family (6). Similar protective roles of nuts against tumorigenesis have also been identified in mice models with cancer xenografts (7). During the multistep development of human tumors, different cancers may share the same biological capabilities (8). Thus, nuts might exert a broad-spectrum anticancer potential, although the exact mechanism has not been fully elucidated.

A number of epidemiologic studies have explored the relationship between nut intake and multiple cancers in the past decades. Since 1992, a lot of case–control studies investigating the associations of nut consumption with different cancers reported both significant and null results (9–11). Growing evidence from cohort studies emerged in recent years (12–14). Interestingly, although most of the studies did not support a strong association between total nut intake and cancer risk, there was a suggestive benefit of tree nuts or peanuts on certain cancers (15–17). Taken together, these studies could not reach a consensus about the relationship regarding nut consumption and cancer. Likewise, in prior meta-analyses, which published before 2016, an inverse association between nut intake and cancer risk was only observed in the pooled estimate of case–control studies, whereas no definite conclusion could be drawn from cohort studies (18, 19).

Given the lack of large-scale intervention studies, prospective investigation may provide promising evidence on the health benefits of dietary nut intake. Since the last meta-analysis was published, 13 new related articles including 20 original cohort studies have been published. It is necessary to update the analysis for a comprehensive

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assessment about this correlation. In this study, we therefore conducted a meta-analysis on published prospective studies to quantify and estimate the effect of nut consumption on cancer risk.

## Materials and Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20).

### Search strategy

A literature search was performed on PubMed and Web of Science databases for articles published online before June 2019. We combined search terms on exposure ("nut" OR "almond" OR "cashew" OR "peanut" OR "pecan" OR "pine nut" OR "pistachio nut" OR "macadamia nut" OR "hazelnut" OR "walnut"), outcomes ("cancer" OR "neoplasm" OR "tumor" OR "carcinoma" OR "malignancy"), and study design ("prospective" OR "cohort" OR "longitudinal" OR "follow-up") without language restriction. We also searched the reference lists of the studies that were included in our analysis as well as those listed in the published meta-analyses for additional studies. Gray literature and unpublished results were not included.

### Study selection

Candidate articles were included if they met the following criteria: (i) applied a prospective design; (ii) evaluated association between nut intake and risk of cancer; (iii) reported estimates of the hazard ratios (HR) or risk ratios (RR) with the corresponding 95% confidence intervals (CI). For dose–response meta-analysis, studies should provide a quantitative measurement of intake, number of cases, and follow-up person-years or total participants for each category (or sufficient data to calculate them) with at least three categories of exposure. If more than 1 study used the same cases in the same cohort, only the study that included the most subjects or had the longest follow-up was included. Retrospective case–control studies, cross-sectional studies, and studies that reported insufficient statistics or results were excluded.

### Data extraction and quality assessment

The following data were extracted from each study: first author's last name; year of publication; study or cohort name; area; follow-up duration; sex of participants; number of cases; number of participants; method of dietary assessment; the maximally adjusted RRs or HRs and corresponding 95% CIs for all categories and covariates adjusted in multivariable analysis. To evaluate the potential dose–response relationship, we further extracted and estimated the median daily intakes as well as number of cases and total participants or follow-up person-years in each nut consumption category. Study quality was assessed with the Newcastle–Ottawa quality assessment scale (21) including selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (9 representing the highest quality). A study was considered to be of high quality if scored more than seven points.

Two authors independently performed the literature search, study selection, and data extraction. The other two independent authors conducted the quality assessment. Any disagreements were resolved by discussion.

### Statistical analysis

HR was directly considered as RR in this meta-analysis. Random effect models were used to estimate summary RRs and 95%CIs for the highest versus the lowest levels of nut intake and for the dose–response analysis. Statistical heterogeneity was assessed with the $Q$ test and $I^2$ statistic. $I^2$ represents the amount of total variation, which is explained by variation between studies, and a value of $\leq$25%, 25%–50%, 50%–75%, and >75% indicates no, low, moderate, and significant heterogeneity, respectively. Subgroup analyses were conducted according to cancer type, geographical area, follow-up time, study quality, and type of nut intake to investigate the associations in certain subjects and to explore the potential sources of heterogeneity. Considering the immediate contact of diet with gastrointestinal tract and the process of diet digestion, we also performed subgroup analysis by dividing the cancers into digestive and nondigestive systems.

We used a previously described method by Greenland and Longenecker (22) and Orsini and colleagues (23) to conduct the dose–response analysis. To perform this analysis, total nut intake was converted from servings (28 grams as a serving size) or other units into grams per day (g/day). The median or mean daily intake of nut in each category was assigned to the corresponding RR with the 95% CI for each study. For studies that reported ranges of nut intake, we estimated the midpoint in each category by calculating the average of the lower and upper boundary. When the highest category was open ended, we assumed the length of the open-ended interval to be the same as that of the adjacent interval. And if the lowest category was open ended, we set the lower boundary to zero. The method described by D. Aune (24) was used to estimate the distribution of person-years in studies that only reported the total number of person-years and distribution of cases. We used restricted cubic splines with 4 knots of the distribution to evaluate potential linear association. A $P$ value for curve linearity or nonlinearity was calculated by testing whether the second and the third regression coefficients were simultaneously equal to zero.

Publication bias was evaluated by Egger test and Begg regression tests, with the results considered to exist obvious publication bias when $P < 0.10$. We carried out sensitivity analysis by excluding one study in turn at a time to clarify whether the result was driven by single one study. All analyses were conducted with STATA version 12.0 (StataCorp LP).

## Results

### Literature search

The process of study identification and selection is presented in **Fig. 1**. Of the 440 articles retrieved from initial search, 420 were excluded after title and abstract screening, and one article with irrelevant exposure was excluded after full-text review. Six articles that met the inclusion criteria were additionally identified by hand searching the reference lists of the 19 eligible articles. Derived from the reference lists of previous meta-analyses, an article (25) reporting all types of cancer was excluded because it was conducted in a subgroup of EPIC cohort that was entirely evaluated in other studies (26–28). Among the above 25 articles, two articles reported sex-specific effect sizes instead of combined estimates, and other two articles provided RRs and CIs in relation to esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia adenocarcinoma, and gastric noncardia adenocarcinoma separately. Therefore, a total of 33 studies from 25 publications (12–17, 26–44) were finally included for our meta-analysis.

### Study characteristics

The characteristics of the included studies are presented in Supplementary Table S1. Overall, 28 prospective cohort studies and 5 case cohort studies incorporating a total of 50,879 cancer cases were

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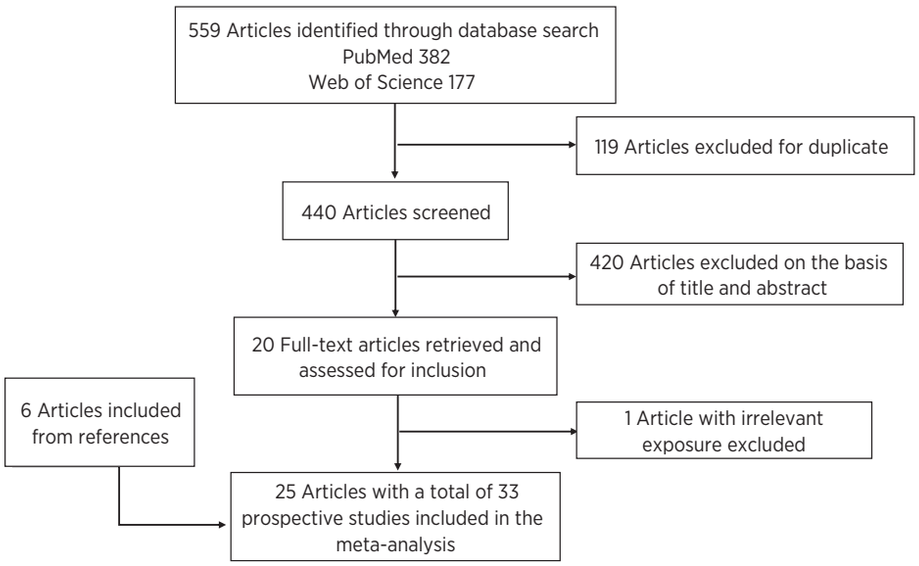


**Figure 1.**
Flow chart of study selection showing literature search for prospective studies of nut consumption in relation to risk of cancer.

evaluated. Thirteen of the studies were conducted in the United States, 16 in Europe, and the other 4 in Asia. Both men and women were included in 17 studies, while 5 studies and 11 studies were conducted in only males or females. The follow-up time ranged from 5.7 to 30 years. Most studies used food frequency questionnaires (FFQ) in dietary assessment except for 9 studies with self-design questionnaires. The major adjusted confounders included age, body mass index, physical activity, alcohol consumption, smoking, education, and total energy intake. The Newcastle–Ottawa Scale (NOS) scores of the included studies ranged from 6 to 9, with 19 high quality studies scored > 7. The risk of nut exposure was evaluated with colorectal cancer (5 studies), esophagus cancer (5 studies), pancreatic cancer (4 studies), gastric cancer (4 studies), breast cancer (4 studies), lung cancer (4 studies), prostate cancer (3 studies), leukemia (1 study), non-Hodgkin lymphoma (1 study), hepatocellular carcinoma (1 study), and ovarian cancer (1 study).

### Meta-analysis

**Figure 2** shows the multivariable-adjusted RRs for each study and the combined RR for the highest versus the lowest category of total nut intake. The summary RR for overall cancer was 0.90 (95% CI: 0.85–0.95; $P < 0.001$) with low heterogeneity across studies ($P\text{-}_{\text{heterogeneity}} = 0.028$; $I^2 = 34.6\%$).

**Figure 3** presents the results of subgroup analysis classified by cancers from digestive and nondigestive system. Intriguingly, the significant inverse association with nut intake was only observed in cancer from digestive system (RR = 0.83; 95% CI, 0.77–0.89; $P\text{-}_{\text{heterogeneity}} = 0.400$) but not in nondigestive cancer (RR = 0.95; 95% CI, 0.89–1.02; $P\text{-}_{\text{heterogeneity}} = 0.036$). Other results of stratified analyses are shown in **Fig. 4**. The relationship between nut intake and cancer risk was significant in Asians and North Americans but not in Europeans. In the subgroup analysis by follow-up duration, studies with longer duration of follow-up time (10–20 years and ≥20 years) presented a significant decline in risk of cancer, while studies with less than 10 years of follow-up showed nonsignificant association. Among the three types of regular nuts (peanuts, tree nuts, and peanut buffer), only tree nut intake was significantly associated with decreased cancer risk (RR = 0.86; 95% CI, 0.77–0.97). In line with results aforementioned, the protective effects of dietary nut consumption against cancer were observed in most of the digestive cancers, including colorectal cancer (RR = 0.81; 95% CI, 0.68–0.96), pancreatic cancer (RR = 0.84; 95% CI, 0.73–0.98), and gastric cancer (RR = 0.79; 95% CI, 0.68–0.91). There was no significant association between consumption of nut and risk of nondigestive cancer types except for lung cancer (RR = 0.86; 95% CI, 0.81–0.91). When we conducted a subset analysis by study quality, significant inverse associations between nut consumption and cancer risk were observed in both high-quality (NOS scores > 7) and low-quality (NOS scores ≤ 7) studies.

### Dose–response analysis

A total of 18 prospective studies (14 publications) with 23,353 cases were included in dose–response analysis. We found an apparent dose–response relationship between amount of daily nut intake and cancer risk with no evidence of significant departure from linearity ($P\text{-}_{\text{nonlinearity}} = 0.930$; **Fig. 5**). A 20 g increment in dietary nut intake was associated with a 10% decrease in risk for cancer (RR = 0.90; 95% CI, 0.82–0.99). The significant protective effect on cancer was manifested when consuming more than 9 g nuts every day (RR = 0.95; 95% CI, 0.91–0.99).

### Publication bias and sensitivity analysis

There was no evidence of publication bias as suggested by both Begg rank correlation test ($P = 0.133$; Supplementary Fig. S1A) and Egger linear regression test ($P = 0.255$; Supplementary Fig. S1B). Sensitivity analyses suggested that the overall risk estimate was not substantially modified by any single study, with the summary estimates narrowly ranging from 0.89 (95% CI: 0.84–0.94) to 0.90 (95% CI: 0.85–0.95; shown in Supplementary Fig. S2A). When studies with a quality score of ≤7 were excluded, a similar result was found: no individual high-quality study had excessive influence on the overall association (Supplementary Fig. S2B).

## Discussion

With a variety of healthy phytochemicals, nuts have been perceived as inhibitors of carcinogenesis. A multiple of hydrophilia compounds (quercetin, resveratrol, and ellagic acid) as well as lipophilic components (tocopherols, tocotrienols, omega-3, and omega-6 fatty acid),

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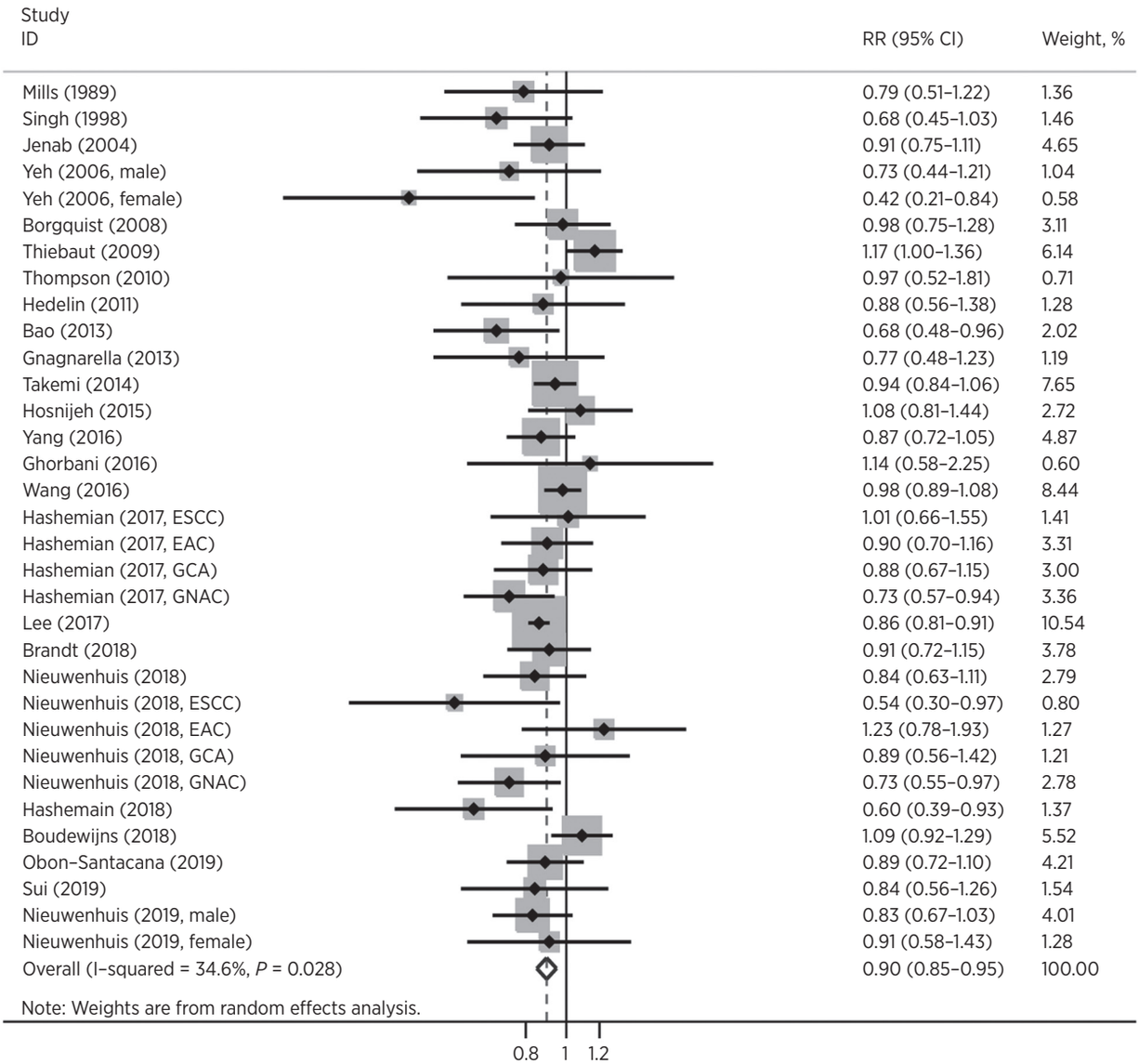


**Figure 2.**

Forest plot of nut consumption and cancer risk. Dots indicate adjusted RRs by comparing the highest with the lowest quantile in nut consumption, and diamonds indicate the pooled RRs. The size of the shaded square is proportional to the percentage weight of each study, and horizontal lines indicate 95% CIs.

which are contained in most of tree nuts, have been shown to exert indirect anticancer activities via their anti-inflammatory and antioxidant actions (45). Besides, it was proposed that bioactive constituents in nuts could directly affect several universal cellular processes in tumor initiation and promotion, such as DNA damage repair, cell differentiation and proliferation, apoptosis, cell invasion, and metastasis (46). According to the hypothesis from Falasca and colleagues, nuts might also inhibit cancer progression through their ability to alter lipid profiles and cell metabolism (47). Herein, it seems plausible that nut consumption might confer a decreased risk of cancer in terms of biological mechanisms.

Numerous epidemiologic studies have investigated the relationship of nut intake and cancer incidence. However, as mentioned above, existing findings are inconclusive. To our knowledge, two prior meta-analyses have evaluated this correlation. On the basis of findings from 20 case–control studies and 11 cohort studies, the first meta-analysis in 2015 revealed a significant inverse correlation of nut consumption and cancer risk in the pooled results of case–control studies (summary RR = 0.82; 95% CI, 0.69–0.98) but not in cohort studies (summary RR = 0.91; 95% CI, 0.81–1.02; ref. 18). The second meta-analysis published in 2016 investigated the relation of nut consumption with multiple health outcomes (19). Nine cohort studies (8 publications) were included to analyze the association between nut intake and cancer (including both cancer morbidity and mortality). However, only one of the 9 studies was conducted to evaluate the relationship of nut consumption and cancer morbidity, while the rest 8 studies were focused on cancer mortality. Although the overall result showed an inverse association between nut intake and cancer (summary RR =

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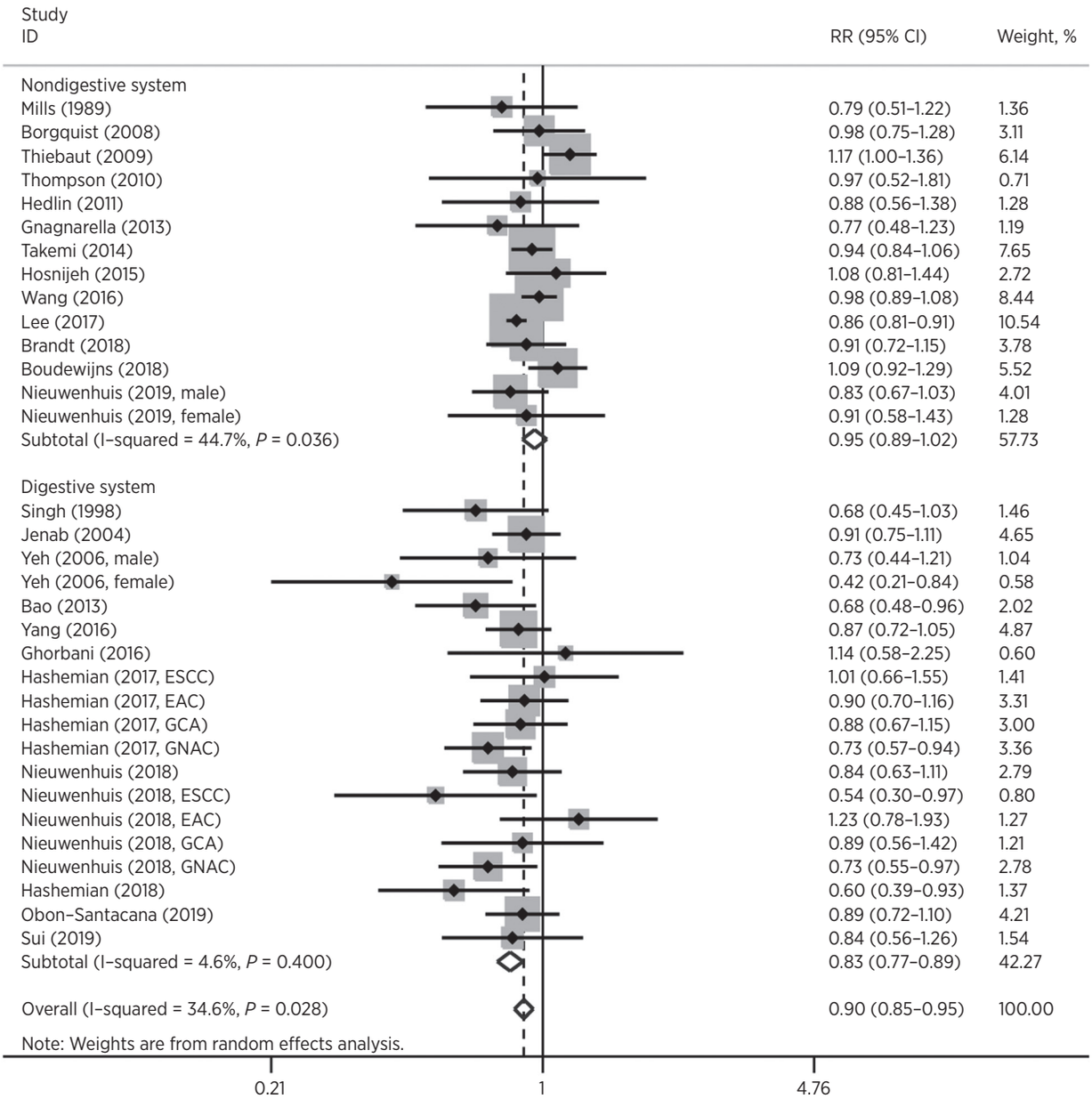


**Figure 3.**
Subgroup analysis stratified by cancer group.

0.82; 95% CI, 0.74–0.89), it was still unclear whether dietary nut intake is associated with cancer incidence. Meanwhile, the meta-analysis was only concerned with the relationship between nut intake and total cancer, while studies reporting specific cancer types were not included.

In this meta-analysis, we reviewed current evidence from 33 prospective studies to give an overall assessment of the relationship between nut intake and cancer risk. Results of this study indicated a linear dose-dependent decrease of cancer risk with the increasing of daily nut intake, and the risk of cancer decreased by 10% for a 20 g/day increment in nut consumption. These findings support the recommendation that 20 g/day (5 servings per week) of nuts, seeds, and soy products intake helps to promote health and prevents chronic diseases in dietary guidelines for Americans (48). We also observed an apparent inverse association between nut consumption and risk of cancers from digestive system with no heterogeneity ($I^2$ = 4.6%), whereas the significant correlation was not found in cancers from nondigestive system. In the following analysis stratified by cancer sites, the inverse relationship persisted significant in most of the digestive cancers including colorectal cancer, pancreatic cancer, and gastric cancer. While in nondigestive cancers, nut intake rendered a preventive effect toward only lung cancer.

Little was known about why nut consumption exerts protective effect against specific cancers. It may be partly explained by joint

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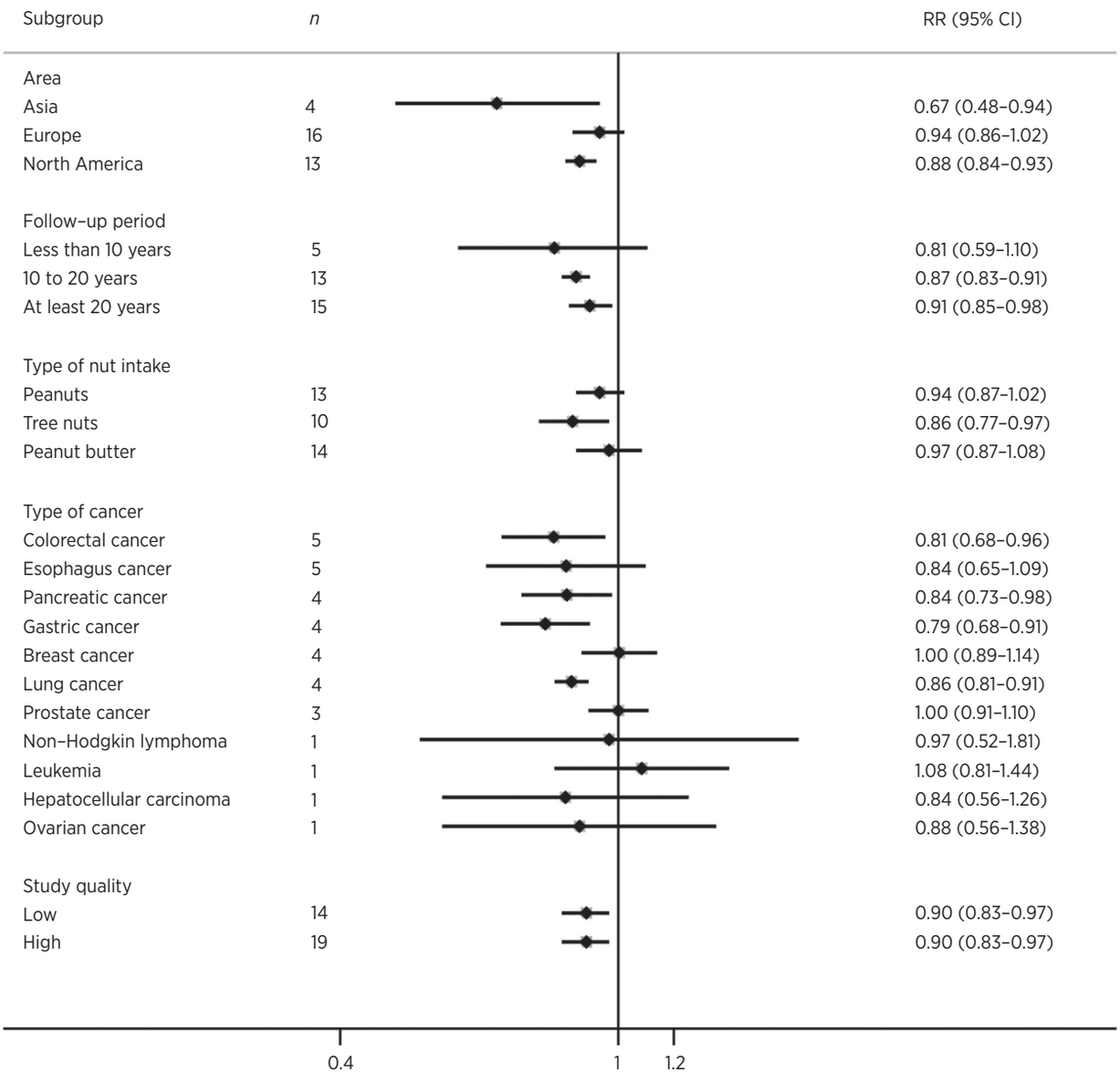


**Figure 4.**
Subgroup analyses stratified by geographical area, duration of follow-up, nut types, cancer types, and study quality. Results were pooled with the use of the random-effects model. *n*, the number of studies included.

actions of multiple compositions in nuts. As an abundant nutrient in nuts, dietary fiber could increase the anaerobic fermentation and reduce the intestinal transit duration, thus might decrease colorectal mucosa's exposure to carcinogens (46). Epidemiologic studies have demonstrated that dietary fiber intake was associated with reduced risks of several cancer types, particularly gastrointestinal cancers (49, 50). In addition to a high content of fiber, nuts are a good source of polyphenols and unsaturated fat. These nutrients were able to increase the abundance of *Bifidobacterium* and *Lactobacillus* in gut, which could suppress gastrointestinal inflammation and carcinogenesis by promoting the production of short-chain fatty acids (51, 52). Coincidentally, emerging evidence from randomized controlled trials (RCT) has proved that walnut and almond ingestion induced changes in the community composition of gastrointestinal microbiota, in which an increase of probiotic- and butyrate-producing bacterium might conduce to the protection against various gastrointestinal diseases and colorectal cancer (53, 54). Ellagic acid in walnuts, pecans, and pine nuts has been shown to inhibit the activation, proliferation, and migration of pancreatic stellate cells (PSC; ref. 55), which play a key role in tumorigenesis and progression of pancreatic adenocarcinoma. Meanwhile, nut intake was found to be associated with decreased insulin levels (56), an important factor in pancreatic cancer development (57). As for lung cancer, there is little *in vivo* and *in vitro* biologic explanation about the protective effect of nut consumption at

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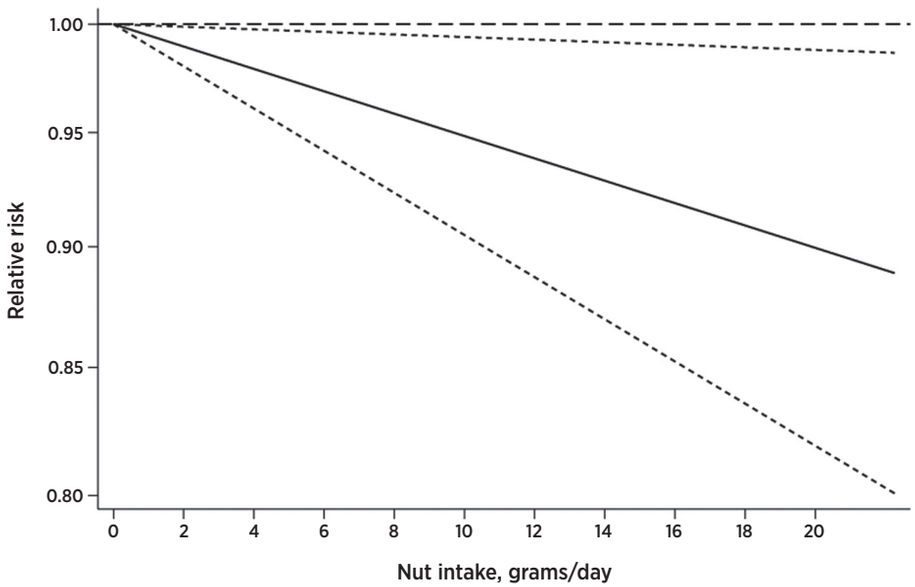


**Figure 5.**
The dose–response analysis of nut consumption with risk of cancer. The solid line and the short dash line represent the relative risk estimates and 95% CIs, respectively. The long dash line is used as reference value of relative risk.

present. Several studies have found that ginkgo biloba exocarp extracts could inhibit tumor angiogenesis and induce autophagy and apoptosis in Lewis lung cancer cells via different signal pathways (58, 59). Besides, a cross-over clinic trial indicated that almond supplementation could reduce oxidative DNA damage and lipid peroxidation in healthy male light smokers, suggesting possible attribution of benefit against smoking-associated lung cancer (60). Taken together, the exact biological mechanisms under the beneficial effects of nut intake on these cancers remain to be elucidated in further researches.

As shown in this study, only the intake of tree nut was in relation to the risk reduction of cancer. This result was consistent with the finding from a meta-analysis stated before (18). A recent randomized trial also showed that an apparent benefit to cancer recurrence and death in patients with stage III colon cancer was confined to consumption of tree nut but not peanut (61). In the Netherlands Cohort Study (NLCS), a nonlinear dose–response relation with pancreatic cancer was found in tree nut intake, but not for total nut, peanut, and peanut butter intake (15). The possible explanation for these results may be attributed to the disparate compositions in different types of nut. Compared with peanut, tree nuts like almonds, cashews, and hazelnuts contain more monounsaturated fatty acids, and walnuts are rich in polyunsaturated fatty acids, especially alpha-linolenic acid (ALA; ref. 5). In addition, bioactive substances vary in different sorts of nut. Specially, α-tocopherol, selenium, phenolic compounds, and phytosterols are abundant in almonds and hazelnuts, Brazil nuts, walnuts, and peanuts, respectively (62). Thus, the anticancer effect of nuts may be diverse according to nut forms. In consideration of the differences in dietary habits and genetic backgrounds, a separate analysis among different populations was performed. Inverse associations of nut consumption and risk of cancer were observed in North American as well as Asian populations, but not in European populations. In the subgroup analysis by follow-up duration, significant inverse associations were observed in studies with a follow-up of 10–20 years and ≥20 years but not in <10 years. It should be interpreted with caution, as the number of cancer diagnosed during a short duration of follow-up was relatively small, thus diminishing the statistical power of the analysis.

Our meta-analysis provides the most up-to-date summary estimates of the association between nut consumption and the risk of cancer. The included studies were well-designed prospective studies with relative high-quality, large sample sizes, and long-term follow-ups. According to sensitivity analyses, associations were robust and significant. Nevertheless, some limitations should be addressed. First, single baseline assessment was used to estimate the dietary nut intake for most of the studies, which could not provide an accurate picture of long-term nut exposure. Although individuals' consumption habits usually do not change easily, repeated assessments are required to obtain the association over time. Second, the assessment of dietary nut consumption was mostly based on self-administered questionnaires instead of accurate measurement, which might give rise to departure from the real situation. Third, the relationships of nut intake with leukemia, non-Hodgkin lymphoma, hepatocellular carcinoma, as well as ovarian cancer were examined in only one study. These associations need further investigations to obtain conclusive results. Finally, effects of some unknown confounding factors cannot be excluded, although the maximally adjusted RRs were adopted in the analyses. For this reason, our results are required to be confirmed in human intervention studies. To date, the only evidence from intervention trial was performed on the Prevención con Dieta Mediterránea (PREDIMED) study, which showed a null effect of the Mediterranean diet with nuts on breast cancer risk (63). Because of the short-term intervention and small number of cases, the anticancer effect of nuts might be limited in that study. Thus, large-scale clinical interventions are warranted to ascertain the effects of long-term nut consumption on cancer risk.

In conclusion, this study provides compelling evidence about the association between nut intake and decreased risk of cancer, especially cancers from digestive system. The significant protective effect of nut intake against cancer was found at a minimum consumption of 9 g per day, and the risk of cancer decreased by 10% for every 20 g/day increase intake of nut. More cancer endpoint trials are needed to support the benefit of nut intake toward cancer prevention.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## Authors' Contributions

**Conception and design:** J. Li, L. Cheng
**Development of methodology:** J. Long
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** J. Long, Z. Ji, P. Yuan, T. Long, K. Liu
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** J. Long, Z. Ji, P. Yuan, T. Long, K. Liu
**Writing, review, and/or revision of the manuscript:** J. Long, J. Li, L. Cheng
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** J. Li, L. Cheng
**Study supervision:** L. Cheng

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