
Sina Naghshi 1, Omid Sadeghi 2, Naemi M., Mohammad Naemi 3, Mehrasa Moezrad 2

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ABSTRACT

Background: This study protocol outlines the planned, systematic review and dose-response meta-analysis of nut intake in relation with cancer risk and its mortality.

Methods: This meta-analysis will be done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). A systematic literature search will be conducted using online databases, including PubMed/Medline, ISI Web of Science, and Scopus with no limitation in language or time of publication to identify observational studies investigating the association of nut intake with cancer risk and its mortality. The target population will be adults (≥18 years of age). Random-effects models will be used to calculate pooled effect sizes (ESs) for the risk of cancer and its mortality based on the comparison between the highest and lowest categories of nut intake and to incorporate variation between studies. Linear and non-linear dose-response analyses will be done to evaluate the dose-response associations between nut intake and risk of cancer and its mortality. The Newcastle-Ottawa Scale (NOS) will be used to assess the risk of bias or quality of included studies.

Conclusion: The findings of this systematic review and dose-response meta-analysis will summarize the available evidence on the association between nut intake and risk of cancer and its mortality.

Keywords: Nut, Cancer, Mortality, Diet, Meta-analysis

Introduction

Cancer is the second leading cause of death globally [1]. Diet has an essential role in the etiology and management of cancer. Several dietary recommendations, such as adherence to healthy dietary patterns, intakes of fruits, vegetables, and fiber-containing foods, have been suggested for decreasing the risk of cancer [2, 3]. Among dietary factors, nuts are the key components of healthy dietary patterns. Nuts are rich sources of anti-tumor components such as antioxidants, fiber, mono/polyunsaturated fatty acids (MUFA/PUFA), and phytosterols [4]. However, the presence of some
carcinogenic compounds such as aflatoxin and added salt may tamper with the anti-carcinogenic properties of nuts [5]. Findings from the previous studies on the association between nut intake and risk of cancer are conflicting. While some investigations documented that total nut intake was associated with a reduced risk of cancer [6, 7], others failed to reach such an association [8, 9]. The same findings exist in the literature about cancer mortality. Some studies revealed that total nut intake was related to a lower risk of cancer mortality [10, 11]; however, some others showed no significant association in this regard [12, 13]. In addition to total nut intake, inconsistent findings are available on the link between tree nut, peanut, and peanut butter consumption and cancer risk and its mortality [14, 15].

Two previously published meta-analyses summarized available findings on the association between nut intake and risk of cancer [16, 17]; however, they had limitations in the inclusion of eligible studies and dose-response meta-analysis. Therefore, a comprehensive meta-analysis is required to summarize available findings on the link between nut intake and cancer risk by considering limitations in the previously published meta-analyses. Hence, this study aimed to describe the protocol of a systematic review and meta-analysis of observational studies which will aim to examine the associations between nut intake and risk of cancer and its mortality were designed.

**Materials and Methods**

This protocol is developed based on Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [18]. The results of this systematic review and meta-analysis will be reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

**Search methods for study identification**

A systematic search using online databases will be conducted, including PubMed/Medline, ISI Web of Science, and Scopus, to identify eligible studies. No limitations in article language or time of publication will be considered. The PubMed search strategies are shown in Table 1.

<table>
<thead>
<tr>
<th>Concept 1</th>
<th>(“nut*” OR “almond” OR “cashew” OR “tree nut” OR “peanut” OR “pecan” OR “pine nut” OR “pistachio” OR “macadamia” OR “peanut butter” OR “hazelnut” OR “walnut”)</th>
</tr>
</thead>
</table>
| Concept 2 | (“neoplasms” OR “carcinoma” OR “cancer” OR “mortality” OR “death” OR “fatal outcome” OR “survival”)

The combination of keywords as mentioned above will be used to search online databases. ("concept 1" AND "concept 2")

**Eligibility criteria**

**Study type**

The published observational studies will be included, with prospective, case-control, case-cohort, or cross-sectional designs, that have reported effect sizes (ESs) including hazard ratios (HRs) or relative risks (RRs) or odds ratios (ORs) with corresponding 95% CIs for cancer or its mortality in relation to nut intake.

**Target population**

The target population will be adults aged 18 years and older. There will be no restrictions on sex, ethnicity, economic status, health status, and education.

**Exposure and outcome variables**

The studies that have considered the intakes of total nut, tree nut, peanut, and peanut butter as the exposure variables and risk of cancer or/and its mortality as the outcome will be included. The studies that have assessed the compounds of nuts
in relation to the risk of cancer will not be included.

Exclusion criteria: Letters to editors, comments, reviews, meta-analyses, ecologic studies, and animal studies will be excluded. The studies that have been conducted on children or adolescents and those that have evaluated the association between nut consumption and cancer survival or cancer recurrence will also be excluded. Moreover, those studies that have evaluated the link between a nut-rich dietary pattern and cancer risk will not be included.

**Data collection and analysis**

Data extraction will be conducted independently by two researchers, and any disagreements will be resolved by consultation with the principal investigator (OS). The following data from each eligible article will be extracted: name of the first author, publication year, study design, location of study, age range, gender, the sample size of the study, number of cases, duration of follow-up (for cohort studies), exposure, methods used for exposure assessment and the diagnosis of cancer, comparison categories, relevant effect sizes (ESs) for cancer or its mortality in relation to nut intake, and confounding variables adjusted in the statistical analysis. If data are reported for men and women separately, each population will be considered as a distinct study. If an included study reports several risk estimates, the fully-adjusted ESs will be extracted.

Assessment of the quality of studies: To determine the quality of the included studies, the Newcastle-Ottawa Scale (NOS), designed for non-randomized studies, will be used [20]. According to this scale, a maximum of nine points would be awarded to each study according to the following parameters: four points for selecting participants, two points for comparability, and three points for the assessment of outcomes. The studies achieving nine points will be considered to provide the highest quality. Studies will not be excluded based on quality assessment. However, a subgroup analysis will be performed to separate the studies with different quality scores.

**Data analysis**

The ORs, RRs, and HRs (and 95% CIs) will be considered the effect sizes of all studies. To calculate the summary effect size for the comparison of the highest versus lowest categories of nut consumption, a random-effects model will be used to take between-study heterogeneity into account. By the random-effects model, both Q-statistic and I² as indicators of heterogeneity will be calculated, and I² will be interpreted according to the Cochrane Handbook thresholds (0-40%, might not be important; 30-60%, might represent moderate heterogeneity; 50-90%, might represent substantial heterogeneity; 75-100%) [21]. In case of significant between-study heterogeneity, subgroup analysis will be conducted based on participants’ gender, duration of follow-up, sample size, geographical location, verification of breast cancer, study design, and adjustment for confounding factors (including energy intake and body mass index) to detect possible sources of heterogeneity. Publication bias will be examined by the use of Begg’s test. A trim-and-fill method will be used to detect the effect of probable missing studies on the overall effect. We will also perform a sensitivity analysis in which each study will be excluded to examine the influence of that study on the overall estimate.

A method suggested by Greenland [22] and Orsini [23] will be used to compute the trend from the OR/RR/HR estimates and their CIs across categories of nut consumption. In this method, the distribution of cases and the ORs/RRs/HRs with the variance estimates for ≥3 quantitative categories of exposure will be required. The midpoint of nut consumption in each category as the corresponding OR/RR/HR estimate will be considered. For the studies that reported the nuts consumption as range, the midpoint in each category by calculating the mean of the lower and upper bound will be
estimated. When the highest and lowest categories are open-ended, the length of these open-ended intervals will be assumed to be the same as that of the adjacent intervals. A two-stage random-effects dose-response meta-analysis will be applied to examine a possible non-linear association between nut consumption and risk of cancer and its mortality. This will be done through modeling of nut consumption and restricted cubic splines with four knots at fixed percentiles of 5, 35, 65, and 95% of the distribution. Based on the Orsini method [23], restricted cubic spline models will be calculated using a generalized least-squares trend estimation method, which will take into account the correlation within each set of reported ORs/RRs/HRs. Then, all the study-specific estimates will be combined with the use of the restricted maximum likelihood method in a multivariate random-effects meta-analysis [24]. A probability value for non-linearity will be estimated using null hypothesis testing in which the coefficient of the second spline was considered equal to 0. In addition to non-linear associations, linear dose-response associations between nut consumption and risk of cancer and its mortality will be investigated using the two-stage generalized least-squares trend estimation method. First, study-specific slope lines will be estimated, and then, these lines will be combined to obtain an overall average slope [23]. Study-specific slope lines will be combined using a random-effects model. Statistical analyses will be conducted using STATA version 14.0. (StataCorp, College Station, Texas, USA) 14.0. P<0.05 will be considered statistically significant for all tests, including Cochran’s Q test.

Discussion

Although several compounds of nuts have been inversely associated with the risk of cancer, the overall association of nut intake with the risk of cancer remains to be clarified. It should be noted that nuts may be contaminated with high concentrations of aflatoxins, which are potent carcinogens and may affect all organ systems, especially the liver and kidneys [5]. Earlier meta-analyses on the association between nut intake and cancer risk reported an inverse association [16, 17]. However, several limitations should be considered in interpreting the results of these meta-analyses. None of these meta-analyses had examined the dose-response association of specific types of nut intake with the risk of overall and specific types of cancer. In terms of cancer mortality, previous meta-analyses revealed an inverse association with nut intake. However, since the release of those meta-analyses, several papers were published on the link between nut intake and cancer mortality. Therefore, evidence in this regard needs to be updated. Moreover, previous meta-analyses on the link between nut intake and cancer mortality did not examine the dose-response associations. Overall, given the above-mentioned points, this study is designed to shed light on the relationships between nut intake and cancer.

Strengths: First, the dose-response analysis will provide the most compelling evidence for the quantitative evaluation of associations and will indicate the shape of possible associations. Also, we will consider different types of nuts, including tree nut, peanut, and peanut butter, which can provide the most comprehensive insight into the association between nut intake and cancer risk. Limitations: Some typical limitations should be noted for the current systematic review and meta-analysis. The observational studies into the current meta-analysis will be included. These types of studies cannot provide conclusive evidence of a causal relationship between nut intake and cancer risk and mortality. Moreover, residual or unmeasured confounding factors may have affected the magnitude of the association between nut intake and cancer risk. Measurement errors in the dietary assessment are inevitable and may be introduced by the under-reporting or over-reporting the amounts of nut intake.

Conclusion

Systematic reviews and meta-analyses are powerful studies that examine diet-disease
associations. The findings of these studies will have great importance for health care systems.

Acknowledgments

None

Authors’ contributions

SN had the initial idea for this review. OS, MN, and MM designed the study, including the development of the selection criteria, the risk of bias assessment strategy, the search strategy and the data extraction strategy. OS and SN prepared the draft of this study protocol. All authors have read and approved the final manuscript.

Support

None

Conflict of Interest

The authors state that there is no conflict of interests in this study.

References


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