

Nut Intake and Risk of Cancer and its Mortality: a Study Protocol for a Systematic Review and Dose-Response Meta-analysis of Observational Studies

Sina Naghshi ¹, Omid Sadeghi ^{2*}, Mohammad Naemi ³, Mehrasa Moezrad ²

Received: 1 July 2020 Accepted: 15 July 2020
Published 2020 Volume 1, Issue 2,


ABSTRACT

Background: This study protocol outlines the planned, systematic review and dose-response meta-analysis of nuts 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 nuts 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

 **How to Cite:** Naghshi S, Sadeghi O, Naemi M, Moezrad M. Nut Intake and Risk of Cancer and its Mortality: a Study Protocol for a Systematic Review and Dose-Response Meta-analysis of Observational Studies. *Critical Comments in Biomedicine*. 2020; 1(2): e10030.

✉ **Omid Sadeghi**
omidsadeghi69@yahoo.com

¹ Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

² Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

³ Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tabriz University of Medical Sciences, Tabriz, Iran

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 1: Medical subject headings (MeSH) and non-MeSH keywords that will be used to search relevant publications on the association between nut intake and cancer

Concept 1	("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")
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 adolescences 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 I^2 as indicators of heterogeneity will be calculated, and I^2 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

- [1] Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. **Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study.** *JAMA oncology.* 2017;3:524-4810.1001/jamaoncol.2016.5688.
- [2] Parohan M, Sadeghi A, Khatibi SR, Nasiri M, Milajerdi A, Khodadost M, et al. **Dietary total antioxidant capacity and risk of cancer: a systematic review and meta-analysis on observational studies.** *Crit Rev Oncol Hematol.* 2019;138:70-8610.1016/j.critrevonc.2019.04.003.
- [3] Nachvak SM, Moradi S, Anjom-Shoae J, Rahmani J, Nasiri M, Maleki V, et al. **Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies.** *Journal of the Academy of Nutrition and Dietetics.* 2019; 119:1483-500.e1710.1016/j.jand.2019.04.011.
- [4] Alasalvar C, Bolling BW. **Review of nut phytochemicals, fat-soluble bioactives, antioxidant components and health effects.** *The British journal of nutrition.* 2015;113 Suppl 2:S68-7810.1017/s0007114514003729.
- [5] Eneroth H, Wallin S, Leander K, Nilsson Sommar J, Åkesson A. **Risks and Benefits of Increased Nut Consumption: Cardiovascular Health Benefits Outweigh the Burden of Carcinogenic Effects Attributed to Aflatoxin B₁ Exposure.** *Nutrients.* 2017; 910.3390/nu9121355.
- [6] Lee JT, Lai GY, Liao LM, Subar AF, Bertazzi PA, Pesatori AC, et al. **Nut Consumption and Lung Cancer Risk: Results from Two Large Observational Studies.** *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2017;26:826-3610.1158/1055-9965.epi-16-0806.
- [7] Yamamura Y, Oum R, Gbito KY, Garcia-Manero G, Strom SS. **Dietary intake of vegetables, fruits, and meats/beans as potential risk factors of acute myeloid leukemia: a Texas case-control study.** *Nutrition and cancer.* 2013;65:1132-4010.1080/01635581.2013.834946.
- [8] Jacobs I, Taljaard-Krugell C, Ricci C, Vorster H, Rinaldi S, Cubasch H, et al. **Dietary intake and breast cancer risk in black South African women: the South African Breast Cancer study.** *The British journal of nutrition.* 2019;121:591-60010.1017/s0007114518003744.
- [9] Obón-Santacana M, Luján-Barroso L, Freisling H, Naudin S, Boutron-Ruault MC, Mancini FR, et al. **Consumption of nuts and seeds and pancreatic ductal adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition.** *Int J Cancer.* 2020;146:76-8410.1002/ijc.32415.
- [10] Guasch-Ferré M, Bulló M, Martínez-González M, Ros E, Corella D, Estruch R, et al. **Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial.** *BMC Med.* 2013;11: 16410.1186/1741-7015-11-164.
- [11] Amba V, Murphy G, Etemadi A, Wang S, Abnet CC, Hashemian M. **Nut and Peanut Butter Consumption and Mortality in the National Institutes of Health-AARP Diet and Health Study.** *Nutrients.* 2019; 1110.3390/nu11071508.
- [12] Luu HN, Blot WJ, Xiang YB, Cai H, Hargreaves MK, Li H, et al. **Prospective evaluation of the association of nut/peanut consumption with total and cause-**

- specific mortality.** *JAMA internal medicine.* 2015;175:755-6610.1001/jamainternmed.2014.8347.
- [13] Eslamparast T, Sharafkhah M, Poustchi H, Hashemian M, Dawsey SM, Freedman ND, et al. **Nut consumption and total and cause-specific mortality: results from the Golestan Cohort Study.** *International journal of epidemiology.* 2017;46:75-8510.1093/ije/dyv365.
- [14] Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. **Association of nut consumption with total and cause-specific mortality.** *The New England journal of medicine.* 2013;369:2001-1110.1056/NEJMoa1307352.
- [15] van den Brandt PA, Schouten LJ. **Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis.** *International journal of epidemiology.* 2015;44: 1038-4910.1093 /ije/ dyv039.
- [16] Long J, Ji Z, Yuan P, Long T, Liu K, Li J, et al. **Nut Consumption and Risk of Cancer: A Meta-analysis of Prospective Studies.** *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2020; 29: 565-7310.1158/1055-9965.epi-19-1167.
- [17] Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. **Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis.** *Nutrition reviews.* 2015;73:409-2510.1093/nutrit/nuv006.
- [18] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.** *Systematic reviews.* 2015;4:110.1186/2046-4053-4-1.
- [19] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.** *Bmj.* 2009;339:b2700 10.1136/ bmj.b2700.
- [20] Peterson J, Welch V, Losos M, Tugwell P. **The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.** *Ottawa: Ottawa Hospital Research Institute.* 2011
- [21] Higgins JP, Green S. **Cochrane handbook for systematic reviews of interventions.** Chichester, England; Hoboken, NJ: Wiley-Blackwell; 2008
- [22] Greenland S, Longnecker MP. **Methods for trend estimation from summarized dose-response data, with applications to meta-analysis.** *American journal of epidemiology.* 1992;135:1301-910.1093/oxfordjournals.aje.a116237.
- [23] Orsini N, Bellocco R, Greenland S. **Generalized least squares for trend estimation of summarized dose-response data.** *The stata journal.* 2006;6:40-57
- [24] Jackson D, White IR, Thompson SG. **Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses.** *Statistics in medicine.* 2010;29:1282-9710.1002/sim.3602.