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LETTER TO THE EDITOR

Nut and peanut butter consumption and risk of prostate cancer in the NIH-AARP diet and health study

Dear Editor,

Prostate cancer is the second most common cancer among men worldwide and leading cancer in incidence among men in the United States (US). In 2018, the US had over 190,000 new prostate cancer cases, accounting for almost 1 in 5 new male cancer diagnoses [1]. A recent review of dietary factors in relation to prostate cancer risk did not find evidence regarding nut consumption as neither a risk nor protective factor, though it has been hypothesized to be associated with a decreased cancer risk through multiple mechanisms [2].

Nuts are nutrient-dense foods that are rich in important macronutrients and bioactive compounds such as unsaturated fatty acids (monounsaturated and polyunsaturated fatty acids), high-quality vegetable protein, fiber, minerals, tocopherols, phytosterols, polyphenols, resveratrol, phenolic compounds, and folic acid [3]. The nutrients in nuts may modify specific processes related to cancer development such as regulation of cell differentiation and proliferation, reduction of tumor initiation/promotion and DNA damage, and regulation of immunologic inflammatory responses [3]. In vitro data also suggests that antioxidant micronutrients protect biomolecules that can influence cancer risk [3, 4].

Prospective analyses in the Health Professionals Follow-up Study, Adventist Health Study, and the Netherlands Cohort, as well as a systematic review, examined total consumption of nuts and peanut butters and reported no association with prostate cancer risk [5–8]. However, two case-control studies showed inverse nut consumption-prostate cancer associations [9, 10]. Differences in study design, sample size and number of events, follow-up time, and source population may explain the discrepant results. Given the limited and inconsistent findings, we examined nut ("peanuts, walnuts, seeds, or other nuts") and peanut butter ("peanut butter or other nut butter") consumption in relation to prostate cancer risk in the prospective National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort.

The median follow-up time for this study was 15.0 years (interquartile range [IQR] = 8.1-15.1 years). Median age of participants at baseline was 63.7 years (IQR = 58.9-67.4 years), with 93.6% being white non-Hispanics. The mean (±standard deviation) nut and peanut butter intake were 3.4 (±9.3) and 3.7 (±8.7) grams per day, respectively. The Pearson correlation between nut and peanut butter consumption was 0.09 ($P < 0.0001$). Baseline characteristics of cohort participants are presented in Supplemental Table S1. Those with higher nut consumption tended to have a higher education level, consumed more calories, ate more meat, drank more alcohol, and had higher monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) intake compared to those with low nut consumption. Higher nut consumers were also less likely to smoke or to have a history of cardiovascular disease, diabetes, heart disease, or hypertension. Those who consumed more peanut butter were more likely to eat meat and have higher MUFA and PUFA intake, and were less likely to drink alcohol.

Multivariable-adjusted models found no association between nut consumption and overall prostate cancer risk (Table 1). Similarly, no significant associations of nut consumption with risk of localized, advanced, or fatal prostate cancers were found. We observed no statistically significant association between peanut butter consumption (categories of peanut butter consumption vs. none) and risk of overall prostate cancer or for aggressiveness subtypes (Table 1).

In the analysis of total nut consumption (nuts and peanut butter combined), we found no association with overall prostate cancer risk. However, there was an inverse association for localized disease (highest versus lowest category, hazard ratio [HR] = 0.77, 95% confidence

Abbreviations: AARP, American Association of Retired Persons; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MUFA, monounsaturated fatty acid; NIH, National Institutes of Health; PUFA, polyunsaturated fatty acid; RR, risk ratio; US, United States

TABLE 1 Hazard ratios and 95% confidence intervals of prostate cancer according to nut intake among participants[†]

	Nut Intake (n = 171,179)						Peanut Butter Intake (n = 171,523)					
Characteristic	**None**	**Tertile 1**	**Tertile 2**	**Tertile 3**	***P*-trend[‡]**	**Continuous[††]**	**None**	**Tertile 1**	**Tertile 2**	**Tertile 3**	***P*-trend[‡]**	**Continuous[‡‡]**
Median nut intake, g/1000 kcal	0	0.12	0.57	2.55	N/A	N/A	0	0.15	0.78	3.71	N/A	N/A
Person-years, *n*	162,143	601,356	602,350	624,987	N/A	N/A	448,342	520,013	505,046	520,897	N/A	N/A
Overall												
Cases (n)	1,390	5,667	5,654	5,707	N/A	N/A	4,055	4,842	4,703	4,850	N/A	N/A
Age-Adjusted HR (95% CI)[§]	1	1.11 (1.05-1.18)	1.12 (1.06-1.19)	1.08 (1.02-1.14)	0.41	0.99 (0.99-1.00)	1	1.04 (1.00-1.09)	1.04 (0.99-1.08)	1.03 (0.98-1.07)	0.93	0.96 (0.90-1.02)
Multivariable-Adjusted HR (95% CI)[¶]	1	1.05 (0.99-1.11)	1.05 (0.99-1.11)	1.00 (0.95-1.07)	0.04	0.99 (0.98-1.00)	1	1.03 (0.98-1.07)	1.02 (0.98-1.07)	1.02 (0.98-1.07)	0.77	0.97 (0.91-1.03)
Localized												
Cases (n)	129	476	488	482	N/A	N/A	357	415	407	401	N/A	N/A
Age-Adjusted HR (95% CI)[§]	1	0.96 (0.79-1.17)	0.98 (0.81-1.19)	0.93 (0.77-1.13)	0.44	0.98 (0.96-1.01)	1	0.99 (0.86-1.14)	1.01 (0.88-1.17)	0.97 (0.84-1.12)	0.60	0.99 (0.80-1.23)
Multivariable-Adjusted HR (95% CI)[¶]	1	0.87 (0.72-1.06)	0.88 (0.72-1.07)	0.83 (0.68-1.01)	0.18	0.99 (0.96-1.01)	1	0.98 (0.85-1.13)	0.99 (0.86-1.15)	0.96 (0.83-1.11)	0.62	1.01 (0.82-1.26)
Advanced												
Cases (n)	146	618	629	637	N/A	N/A	431	551	500	555	N/A	N/A
Age-Adjusted HR (95% CI)[§]	1	1.15 (0.96-1.38)	1.18 (0.99-1.42)	1.14 (0.95-1.37)	0.86	1.00 (0.98-1.02)	1	1.12 (0.99-1.27)	1.04 (0.91-1.18)	1.11 (0.97-1.25)	0.37	1.01 (0.84-1.21)
Multivariable-Adjusted HR (95% CI)[¶]	1	1.11 (0.92-1.33)	1.13 (0.94-1.36)	1.09 (0.90-1.30)	0.84	1.00 (0.98-1.02)	1	1.10 (0.97-1.25)	1.02 (0.89-1.16)	1.09 (0.96-1.24)	0.41	1.02 (0.84-1.23)
Fatal												
Cases (n)	73	211	211	235	N/A	N/A	158	187	182	205	N/A	N/A
Age-Adjusted HR (95% CI)[§]	1	0.81 (0.62-1.06)	0.84 (0.65-1.10)	0.88 (0.68-1.15)	0.68	1.01 (0.97-1.04)	1	1.07 (0.86-1.32)	1.04 (0.84-1.29)	1.11 (0.90-1.37)	0.39	1.05 (0.77-1.41)
Multivariable-Adjusted HR (95% CI)[¶]	1	0.84 (0.64-1.11)	0.89 (0.68-1.17)	0.93 (0.71-1.22)	0.50	1.01 (0.97-1.04)	1	1.04 (0.84-1.29)	1.00 (0.81-1.24)	1.08 (0.88-1.34)	0.46	1.05 (0.77-1.42)

[†]Intake density is based on gram per 1000 kcal.

[‡]Median value was used to assess linear trend.

[§]Age-adjusted model adjusted for age (years).

[¶]Multivariable model adjusted for age (continuous, years), BMI (continuous, kg/m^2), calories (continuous, kcal/day), educational level (less than high school, completed high school, post-high school or some college, college and postgraduate), smoking status (never, former ≤20 cigarettes/day, former >20 cigarettes/day, current ≤20 cigarettes/day, current >20 cigarettes/day), physical activity (never/rarely, 1-3 times/month, 1-2 times/week, 3-4 times/week, ≥5 times/week), race (non-Hispanic white, non-Hispanic black, other), self-reported health (excellent/very good, good, poor/fair), cardiovascular disease, marital status, prostate cancer screening, family history of prostate cancer and daily intakes of vegetable, fruit, and alcohol (continuous).

[††]Every quarter cup or 32.75 g/1000 kcal.

[‡‡]Every 1 tablespoon or 16 g/1000 kcal.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index, N/A, not applicable.

interval [CI] = 0.60-0.99), although with a non-statistically significant trend (*P*-trend = 0.36). There was no association of total nut consumption with neither advanced nor fatal prostate cancer (Supplemental Table S2).

After multivariable adjustment, greater frequency of nut consumption (>3-4 times per week) was inversely associated with overall prostate cancer risk (HR = 0.92, 95% CI = 0.87-0.97), when compared with the lowest frequency (less than 1 time per month; *P*-trend = 0.005; Supplemental Table S3). This appeared driven by the association with advanced disease. Peanut butter consumption frequency was not associated with overall prostate cancer or with aggressiveness subtypes. Further adjustment for height, intakes of dairy and calcium in the models did not change our results (Supplemental Table S4 and Supplementary Table S5). Additional models that excluded body mass index (BMI) and dietary variables to avoid possible over adjustment yielded similar findings (Supplemental Table S6 and Supplemental Table S7). Further, no statistically significant associations between nut or peanut butter consumption and risk of prostate cancer across subgroups of selected factors, including age, BMI, race, educational level, and prostate cancer screening were observed (**data not shown**).

In this large prospective cohort study with 16-years of follow-up, we did not observe an association between nut or peanut butter consumption and risk of prostate cancer overall, though there was evidence of an inverse association between total nut consumption and localized disease, as well as between greater frequency of nut consumption and overall prostate cancer risk. To our knowledge, this is the largest prospective study to examine the associations between nut and peanut butter consumption and overall and stage-specific prostate cancer. Of note, the National Health and Nutrition Examination Survey (NHANES) 2005-2010 reported an average nut consumption of 3.3 g per day [11], similar to that in NIH-AARP of 3.4 g per day.

The null nut consumption-overall prostate cancer association reported here is largely consistent with previous prospective cohort data, i.e., the Adventist Health Study, with men followed for up to only six years, showed no association between current consumption of nuts and prostate cancer risk [6], the Health Professionals Follow-up Study also concluded that there was no association between nut consumption and prostate cancer incidence (HR = 0.98, 95% CI = 0.89-1.09, *P*-trend = 0.61), although a possible association with frequency of consumption was indicated [5], and the Netherlands Cohort Study also reported no nut consumption-prostate cancer risk association (HR = 1.09, 95% CI = 0.92-1.29, *P*-trend = 0.41) [7]. Furthermore, a recent dose-response meta-analysis (n = 6 studies) found no statistically significant association between total nut intake and risk of prostate cancer; suggesting a limited number of studies available for analysis, and highlighting the importance of additional prospective large cohort studies to re-examine these associations [8]. The unique aspects of our analysis compared to prior studies, which include the largest sample size to date affording robust examination of population subgroups and our finding of an inverse association for more frequent nut consumption. We had extensive data on potential confounding factors and cancer diagnoses. Although there was no association between overall nut consumption and prostate cancer risk overall, associations for consumption of specific nuts (e.g., almonds, Brazil nuts, cashews, hazelnuts, pecans, pistachios, and walnuts) were not examined and remain unclear but relevant.

Our study suggests that the highest frequency nut consumption (>3-4 times per week) may be related to a lower risk of overall prostate cancer and that higher total nut consumption could be associated with a lower risk of localized prostate cancer. We attribute the difference in the prostate cancer risk association between frequency and total consumption amount to the potentially lower inherent measurement error for frequency of consumption as compared with total gram consumption which is additionally calculated from estimated portion size. Effectively, the combined measurement errors from two factors (portion size and frequency) compared to one remain subject to greater non-differential misclassification of nut consumption which may have biased those associations toward the null.

In conclusion, nut and peanut butter consumption were not associated with prostate cancer risk in this large prospective cohort analysis. However, more frequent nut consumption of >3-4 times per week was associated with significantly reduced risk. Consumption of specific nut types or additional preparations of nuts were not queried specifically in our study; therefore, additional prospective investigations with more detailed nut consumption data are warranted to arrive at a more complete determination of the nut consumption-prostate cancer association. Additionally, re-examination of the observed inverse association for more frequent nut consumption and prostate cancer risk is warranted.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, and all participants provided written informed consent.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The study utilized data from the NIH-AARP Diet and Health Study and is publicly accessible to qualified investigators.

COMPETING INTERESTS

None of the authors reported a conflict of interest related to this study.

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AUTHORS' CONTRIBUTIONS

DA and JH designed the study and methodology. MT and JH analyzed and interpreted the data. MT, LMF, SJW, MH, DA, and JH wrote and revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30.
2. Research WCRFIAIfC. Diet, nutrition, physical activity and prostate cancer. Continuous Update Project Expert Report 2018. 2018.
3. Gonzalez CA, Salas-Salvado J. The potential of nuts in the prevention of cancer. Br J Nutr. 2006;96(Suppl 2):S87–94.
4. Greenwald P, Clifford CK, Milner JA. Diet and cancer prevention. Eur J Cancer. 2001;37(8):948–65.
5. Wang W, Yang M, Kenfield SA, Hu FB, Stampfer MJ, Willett WC, et al. Nut consumption and prostate cancer risk and mortality. Br J Cancer. 2016;115(3):371–4.
6. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer. 1989;64(3):598–604.
7. Boudewijns EA, Nieuwenhuis L, Geybels MS, van den Brandt PA. Total nut, tree nut, peanut, and peanut butter intake and the risk of prostate cancer in the Netherlands Cohort Study. Prostate Cancer and Prostatic Diseases. 2019;22(3):467–74.
8. Naghshi S, Sadeghian M, Nasiri M, Mobarak S, Asadi M, Sadeghi O. Association of Total Nut, Tree Nut, Peanut, and Peanut Butter Consumption with Cancer Incidence and Mortality: A Comprehensive Systematic Review and Dose-Response Meta-Analysis of Observational Studies. Adv Nutr. 2021;12(3):793–808.
9. Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutr Cancer. 1999;34(2):173–84.
10. Raimondi S, Mabrouk JB, Shatenstein B, Maisonneuve P, Ghadirian P. Diet and prostate cancer risk with specific focus on dairy products and dietary calcium: a case-control study. Prostate. 2010;70(10):1054–65.
11. O'Neil CE, Nicklas TA, Fulgoni VL, 3rd. Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National Health and Nutrition Examination Survey 2005-2010. Nutrients. 2015;7(1):595–607.

SUPPORTING INFORMATION

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