Nut And Peanut Butter Consumption And Risk Of Prostate Cancer In The Nih-Aarp Diet And Health Study

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NUT AND PEANUT BUTTER CONSUMPTION AND RISK OF PROSTATE CANCER IN THE NIH-AARP DIET AND HEALTH STUDY

By Trucmai (Mimi) Ton

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ABSTRACT

Background: While nuts and their related nutrients have been inversely associated with some cancers, the association between nut consumption and prostate cancer has been inconsistent.

Methods: We conducted an analysis of the association between nut and peanut butter consumption and risk of incident prostate cancer among 173,243 men in the prospective NIH-AARP Diet and Health Study. There was a total of 18,619 incident prostate cancer cases during the 16 years of follow-up. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression for intake of nuts, peanut butter, and total nuts (nuts plus peanut butter), as well as frequency of nut consumption. We evaluated associations with overall prostate cancer and the following subtypes: adenocarcinoma, localized, advanced, fatal, low-grade (Gleason 2-7), and high-grade (Gleason ≥8).

Results: There was no association between nuts (highest versus lowest category HR=1.00, 95% CI: 0.95, 1.07), peanut butter consumption (HR=1.02, 95% CI: 0.98, 1.07), or total nuts (HR=1.00, 95% CI: 0.93, 1.09) and prostate cancer. Similarly, there were no associations with nuts, peanut butter, and total nuts localized, advanced, or fatal prostate cancer in this population. There was some evidence of an inverse association for frequency of nut consumption and prostate cancer (highest versus lowest category HR=0.93, 95% CI: 0.88, 0.98), but the p-trend was not statistically significant (0.07).

Conclusions: In this large prospective cohort study, there was no clear evidence for an association between nut or peanut butter consumption and prostate cancer. Additional research in prospective studies with detailed information on nut consumption is warranted given the lack of data on this association.
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INTRODUCTION

Prostate cancer is the second most common cancer among men worldwide and the leading cancer among US men. In 2018, the US had over 170,000 new prostate cases, accounting for almost 1 in 5 new male cancer diagnoses [1]. A recent review of dietary risk factors in relation to prostate cancer did not find evidence to place nut consumption as a clear risk factor or as a protective factor [2]. However, nuts have been hypothesized to be associated with a decreased risk of cancer through multiple mechanisms [2, 3].

Nuts are nutrient dense foods that are rich in important macronutrients and bioactive compounds, such as unsaturated fatty acids (MUFA$s$ and PUFA$s$), high-quality vegetable protein, fiber, minerals, tocopherols, phytosterols, and phenolic compounds [4, 5]. The nutrients in nuts may modify specific processes related to cancer development, such as the regulation of cell differentiation and proliferation, reduction of tumor initiation or promotion, DNA protection, and regulation of immunologic inflammatory responses [4]. Specifically, flavonoids metabolize and facilitate the elimination of potentially cancerous chemical compounds or their metabolites, while antioxidant micronutrients may protect against oxidative damage [4, 6]. In vitro data also suggests that antioxidant micronutrients protect biomolecules that can influence the risk for cancer development [4, 6]. Additional nutrients found in nuts have other cancer preventative effects, such as polyphenols which inhibit chemically induced carcinogenesis, folic acid which reduces DNA damage, and resveratrol which regulates inflammatory response and immunological activity [7]. Numerous experimental studies in animals and cultures of cell lines have also indicated that vitamin E, a micronutrient found in high amounts in nuts, can regulate differentiation and proliferation [6].
Epidemiologic studies have found inverse associations between nut consumption and risk of gastric, esophageal, and lung cancers \cite{8, 9}. Nut consumption has also been associated with a reduced risk of cancer incidence, cancer death, and all-cause mortality \cite{7, 10}. For prostate cancer, a cross-national study found that prostate cancer mortality was inversely associated with the consumption of nuts and oilseeds \cite{3}. Two previous case-control studies indicated that increasing nut consumption was inversely associated with prostate cancer; yet, the studies did not include consumption on nut butters \cite{11, 12}. However, two prospective cohort studies in the Health Professionals Follow-up Study found no such association \cite{13, 14}. Based on the limited research on this topic, in this study we examined nut and nut butter consumption in relation to prostate cancer risk in the prospective National Institutes of Health (NIH)-AARP Diet and Health Study cohort.

**MATERIALS AND METHODS**

**Study Population**

The NIH-AARP Diet and Health Study is a prospective cohort study established in 1995 to 1996 \cite{15}. The cohort enrolled US adults between the ages of 50 and 71 years residing in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI). The self-administered baseline questionnaire (BQ) and risk factor questionnaire (RFQ) assessed demographics, lifestyle, and medical characteristics. 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.
A total of 566,407 participants satisfactorily completed the BQ after excluding additional withdrawals (n=1), duplicate records (n=179), subjects who moved out of study area before returning BQ (n=321) or were found to have died before study entry (n=261). The RFQ was mailed to BQ participants without baseline self-reported colon, breast, or prostate cancers for additional epidemiologic info in 1996 to 1997. A total of 334,905 participants completed the RFQ after accounting for participants who withdrew from the study (n=3), died (n=1,619), or moved out of the study area (n=547) before the RFQ. For this analysis, women (n=161,432) were omitted leaving a population of 175,644 men who satisfactorily completed both the BQ and RFQ. Further removal of those with follow-up time of less than 0.05 years (n=2,401) left 173,243 men. Finally, after excluding those who did not provide information on nut (n=2,064) and nut butter (n=1,720) intake, the final analytic populations included 171,179 and 171,523 men for the two dietary exposures, respectively.

Assessment of Dietary Factors

At baseline, participants completed a validated 124-item food-frequency questionnaire regarding dietary intake over the previous 12 months. [16]. Participants were asked how often they consumed nuts or nut butter, with regard to both portion size and frequency. Nut consumption was defined as “peanuts, walnuts, seeds, or other nuts” measured in one-fourth cup increments and peanut butter consumption was defined as “peanut butter or other nut butter” measured in tablespoon increments. The frequency categories ranged from never to ≥2 times per day, while portion sizes were less than ¼ cup to more than ½ cup for nuts and less than 1 tablespoon to more than 2 tablespoons for nut butter. We used the following USDA conversions
from grams for nuts and nut butter: quarter cup of nuts equal to 32.7 grams and one tablespoon of nut butter equal to 16 grams.

**Ascertainment of Prostate Cancer and Cohort Follow-up**

Cancer registry linkages from eight states (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Georgia, and Michigan) were conducted to obtain cancer diagnosis information. The analyses in the study were completed for the following categories of incident prostate cancer: overall, adenocarcinoma, localized, advanced, fatal, low-grade (Gleason 2-7), and high-grade (Gleason ≥8). Overall incident prostate cancer (n=18,619) was defined by registry confirmation, Surveillance, Epidemiology and End Results (SEER) mid-level detail cancer site group of first registry reported cancer, and SEER cancer site code in accordance with the International Classification of Diseases for Oncology (ICD-O-3). The cancer endpoint is defined as carcinoma in situ via the cancer registry, 26 in the SEER cancer site group of first registry, C619 in the ICD-O-3 cancer site group, and 28010 in the SEER cancer site recode in ICD-O-3. Localized prostate cancer was defined as stage T1 or T2, N0, M0 and Gleason score of 2-7 at diagnosis (n=1,590) while advanced prostate cancer was defined as stage T3 or T4, N1, M1, or Gleason score of 8 or more at diagnosis (n=2,502). Fatal cancer was defined as those with a cause of death listed as prostate cancer death in the NDI (n=738).

Participants from the NIH-AARP Diet and Health Study were followed from the return of the RFQ until diagnosis, death, relocation outside the registry ascertainment area, or December 31, 2011. Changes in address through linkage were assessed with the US Postal Service, while vital status were assessed through the National Death Index (NDI) and Social Security Administration (SSA).
**Statistical Analysis**

Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CI) between nut and nut butter consumption and prostate cancer incidence. Person-years was used as the underlying time metric and was computed from the date of receiving a valid RFQ until the date of cancer diagnosis, death, relocation outside ascertainment area, or follow-up end (December 31, 2011), whichever occurred first. Using the Cox regression model and Kaplan-Meier curves, we evaluated the proportional hazards assumption.

Dietary variables were energy-adjusted using the multivariate nutrient dense method. Categorical cut-points for nut, peanut butter, and total nut (nut plus peanut butter) consumption were based on intake in the analytic cohort, with the first category serving as the referent. The first category contained non-consumers while the other three categories are based on tertiles of consumption of nut or peanut butter consumption among consumers of each of these foods. The median of each category was used to evaluate linear trend. We also assessed the association using continuous intake measures (1/4 cup for nut consumption and 1 tablespoon for nut butter consumption). Finally, we examined the association between frequency of nut and peanut butter consumption in relation to prostate cancer. Categorical cut-points were based on the FFQ categories (never to 1-6 times per year, 7-11 times per year to 1 time per month, 2-3 times per month to 1-2 times per week, and 3-4 times per week to 2+ times per day).

We calculated HRs and 95% CI for age-adjusted and multivariate-adjusted models. Our multivariate models included age, vegetable intake, fruit intake, body mass index (BMI), calories, alcohol consumption, education level, smoking status, physical activity, race, self-reported health status, cardiovascular disease, diabetes, marriage status, prostate cancer screening
history, and family prostate cancer history. We also evaluated the Healthy Eating Index 2010 (HEI 2010), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids intake, multivitamin use, fiber, dairy, history of stroke, red meat consumption, height, calcium, beta-carotene, alpha-tocopherol, selenium, supplement vitamin D, vitamin D, supplement vitamin E, and vitamin E as potential confounders, but as these variables did not alter risk estimates by 10% or more, they were not included in the final multivariate model.

To assess the potential for reverse causality, we conducted a sensitivity analysis in which we removed the first two years of follow-up. We also evaluated interactions between nut consumption and age, BMI, race, education, and prostate cancer screening status with likelihood ratio tests. The statistical significance cutoff for the interaction likelihood ratio test was a P-value of <0.05.

All statistical analyses were performed using SAS software (Version 9.4). All P-values were 2-sided, and a P-value of <0.05 was considered statistically significant.

RESULTS

Our population had a median follow-up time of 15.0 (IQR=8.1-15.1) years. The median age of 173,243 males in our analytic sample was 63.7 (IQR=58.9-67.4) years, with 93.6% identifying as non-Hispanic white. The mean nut and peanut butter intake among consumers were 3.4 ± 9.3 and 3.7 ± 8.7 grams per day, respectively. The correlation between nut and peanut butter consumption was 0.09 (p-value <0.0001).

As shown in Table 1, in general those with higher nut consumption were more likely to drink more alcohol, have a higher level of education, be more active, eat more meat, consume more calories, and have higher MUFA and PUFA intake compared to those with low nut
consumption. They were also less likely to smoke or to have a history of cardiovascular disease, diabetes, heart disease, and hypertension. Those who consumed more peanut butter were more likely to drink less alcohol, eat more meat, and have higher MUFA and PUFA intake.

The associations between nut consumption and risk of prostate cancer are shown in Table 2. In our fully adjusted models, there was no association between nut consumption and overall prostate cancer (highest versus lowest category HR=1.00, 95% CI: 0.95, 1.07). Similarly, no statistically significant associations between nut consumption and risk of localized, advanced, or fatal prostate cancer were observed.

The associations between peanut butter consumption and risk of prostate cancer are shown in Table 3. We did not observe any statistically significant associations between peanut butter consumption and risk of overall prostate cancer (highest versus lowest category HR=1.02, 95% CI: 0.98, 1.07) or for risk of the subtypes of prostate cancer we evaluated.

Total nut intake (nut and peanut butter) and risk of prostate cancer is summarized in Table 4. We did not observe an association between total nut intake, and overall prostate cancer (highest versus lowest category HR=1.00, 95% CI: 0.94, 1.09). There was an inverse association between total nut intake for the top category of nut consumption compared to no nut intake and localized prostate cancer (HR: 0.77, 95% CI: 0.60, 0.99). However, the p-trend was not statistically significant (p-trend=0.36). There was also no association between total nut intake and risk of advanced or fatal prostate cancer.

Nut consumption frequency was inversely associated with risk of overall prostate cancer for the higher versus the lowest category (HR: 0.93, 95% CI: 0.88, 0.98), with a borderline statistically significant p-trend (0.07) (Table 5). There was no association between nut frequency
and any of the prostate cancer subtypes. We also assessed absolute nut intake in which nut intake was not energy adjusted and found no statistically significant associations (data now shown).

To account for reverse causality, the association between nut and peanut butter intake, and risk of prostate cancer was examined after exclusion of the first two years of follow-up (Supplemental Table 1). This sensitivity analysis did not alter the results.

There were no statistically significant interactions with age, BMI, race, screening status, education attainment, and family history of prostate cancer, and nut intake (data not shown).

**DISCUSSION**

In this large prospective cohort study, we did not observe an association between nut and peanut butter intake and risk of overall prostate cancer. There was limited evidence of an inverse association with the highest category of total nuts and localized prostate cancer as well as the highest level of nut consumption frequency and overall prostate cancer, but the linear trends were not statically significant for both of these measures of nut consumption. To our knowledge, this study is the largest prospective study to examine the association for nuts and peanut butter in relation to overall prostate cancer and by prostate cancer subtypes.

Previous studies have found an inverse association between nut consumption and other cancers including gastric, esophageal, and lung [8, 9]. However, inconsistent results have been observed for prostate cancer. An analysis that combined three case-control studies in Canada found that increasing intake of combined beans, lentils, and nuts was inversely associated with risk of prostate cancer (OR: 0.69; 95% CI: 0.53-0.91) [11]. Given that nuts were combined with other foods in this study, the results are difficult to compare to other studies. In another case-control study in Canada, nut intake greater than 3.0 grams a day associated with decreased
prostate cancer risk (OR: 0.43; 95% CI: 0.22-0.85) [12]. It is important to consider that these case-control studies are potentially subject to recall bias. Our largely null results align with two prior prospective studies among Adventist men in California [14] and men in the Health Professionals Follow-up Study [13]. The study of Adventist men was limited by a small number of cases (n=180) and both of these existing cohort studies evaluated intake as frequency of nut consumption only and did not include nut butters.

We did observe some limited evidence of an inverse association with the highest level of total nuts and localized prostate cancer, and most frequent nut consumption category and overall prostate cancer. However, for each of these associations, there was no statically significant linear trend. While we did not evaluate this in the present study, there are some data to support an inverse association between nut consumption after prostate cancer diagnosis and all-cause mortality from the Health Professionals Follow-Up Study [17]. Nut consumption has also been associated with a reduced risk of overall cancer incidence and cancer death, and all-cause mortality [7, 10].

There are multiple hypotheses surrounding potential anticancer properties of nuts. Growing evidence of the role of inflammation and oxidative stress in the development of specific cancer types point toward antioxidative and anti-inflammatory properties of nuts as a mechanism [18]. In vitro data has shown that antioxidant micronutrients may protect against oxidative damage thereby impacting cancer development [6]. Other nut phytochemicals have also been shown to have anticancer properties. Resveratrol induces apoptosis, inhibits cell invasion, and angiogenesis in in vivo models for breast, colorectal, liver, pancreatic, and prostate cancer through the inhibition of molecular targets [18, 19]. Phytoestrogens also act as estrogen
antagonists that may have protective action in hormone-dependent diseases, including prostate, breast, and bowel cancer [18].

The strengths of this study include the large sample size, prospective design, and long follow-up time that increased our power to detect even modest associations. We also had extensive data on dietary and lifestyle factors to assess for potential confounders. Our data on nut consumption included both frequency and portion size, and included questions on nuts as well as peanut butter. Furthermore, we had detailed disease data to be able to evaluate total prostate as well as prostate cancer subtypes. Further strengths include no recall bias, which may explain some of the differences between the cohort and case-control findings pertaining to this association, and the ability to assess reverse causality.

Our study also had some limitations. We only had dietary data from one timepoint, so we could not assess the impact of changes in nut consumption over time. While our models accounted for numerous potential confounders, residual confounding might still be present. The generalizability of the cohort is also limited as the majority of the NIH-AARP study is non-Hispanic white. Furthermore, while the FFQ was expansive, it did not ask participants to report on different types of nuts separately. In addition, FFQs are subject to nondifferential misclassification which may have biased our results toward the null.

In conclusion, nut and peanut butter consumption were not clearly associated with prostate cancer risk in this large prospective cohort. Additional prospective studies with detailed nut consumption data are still warranted to clarify this association, as few studies have addressed this question.
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TABLE 1 Baseline characteristics of participants by categories of dietary nut and peanut butter intake in the NIH-AARP Diet and Health Study\(^1\)

| Nut Intake (n=171,179) | Peanut Butter Intake (n=171,523) |
|------------------------|----------------------------------|
| C1 (n=14,570)          | C2 (n=51,854)                    |
| C3 (n=51,537)          | C4 (n=53,218)                    |
| C1 (n=38,528)          | C2 (n=44,279)                    |
| C3 (n=43,545)          | C4 (n=45,171)                    |
| **Nut or peanut butter intake, g/1000 kcal** | **Age at baseline, y** |
| 0                      | 63.9 (59.0, 67.3)                |
| 0.12 (0.06, 0.19)      | 63.3 (58.5, 67.0)                |
| 0.57 (0.43, 0.77)      | 62.7 (57.9, 66.6)                |
| 2.55 (1.57, 4.64)      | 63.1 (58.3, 66.8)                |
| 0                      | 63.4 (58.5, 67.0)                |
| 0.15 (0.09, 0.25)      | 62.7 (57.8, 66.7)                |
| 0.78 (0.54, 1.09)      | 63.1 (58.2, 66.8)                |
| 3.71 (2.41, 6.99)      | 63.4 (58.6, 66.9)                |
| **BMI, kg/m\(^2\)**    |                                 |
| 26.3 (24.1, 29.2)      | 62.7 (24.1, 29.2)                |
| 26.5 (24.3, 29.1)      | 26.6 (24.5, 29.4)                |
| 26.6 (24.4, 29.2)      | 26.2 (24.2, 28.7)                |
| 26.6 (24.4, 29.3)      | 26.6 (24.4, 29.3)                |
| 26.6 (24.4, 29.3)      | 26.6 (24.4, 29.3)                |
| **Race**               |                                 |
| Non-Hispanic White     | 93.3                             |
| Non-Hispanic Black     | 93.7                             |
| Other                  | 94.3                             |
| **Smoking**            |                                 |
| Never                  | 26.5                             |
| Former                 | 26.6                             |
| ≤20 cigarettes/d       | 26.6                             |
| >20 cigarettes/d       | 31.0                             |
| Current                | 6.6                              |
| ≤20 cigarettes/d       | 5.3                              |
| >20 cigarettes/d       | 3.9                              |
| **Education, %**       |                                 |
| Less than high school  | 8.6                              |
| Completed high school  | 29.4                             |
| Post-high school or some college | 22.2 |
| College and postgraduate | 37.0 |
| **Physical activity, %** |                                 |
| Never/Rarely           | 20.4                             |
| 1-3 times/mo           | 11.3                             |
| 1-2 times/wk           | 17.0                             |
| 3-4 times/wk           | 25.9                             |
| ≥5 times/wk            | 24.8                             |
| **Calories, kcal/d**   | 1730 (1305, 2279)                |
| Vegetable intake, servings/d | 3.2 (2.1, 4.9)            |
| Fruit intake, servings/d | 2.4 (1.3, 4.0)                  |
| Red meat intake, g/d   | 49.2 (22.2, 89.2)                |
| Alcohol, g/d           | 1.5 (0, 12.2)                    |
| MUFA intake, g/d       | 18.9 (12.6, 28.2)                |
| PUFA intake, g/d       | 11.2 (7.8, 16.2)                 |
| **HEI 2010**           | 65.1 (55.7, 72.6)                |
| **Self-reported history, %** |                                 |
| Heart disease          | 26.3                             |
| Diabetes               | 13.5                             |
| Stroke                 | 3.4                              |
| Hypertension           | 45.2                             |
| Screening              | 84.3                             |
| Prostate cancer family history, % | 7.1 |

**NOTE:** Some percentages do not sum to 100 due to missing data and rounding.

\(^1\) Values are presented as either median (IQR) or percentages. Intake density is based on gram per 1000 kcal. C, category. HEI 2010, Healthy Eating Index 2010.
TABLE 2 Hazard ratios and 95% confidence intervals for risk of prostate cancer associated with nut intake (N=171,179)\(^1\)

| Nut Intake | C1 | C2 | C3 | C4 | P for trend\(^2\) |
|------------|----|----|----|----|------------------|
| Median nut intake, g/1000 kcal | 0  | 0.12 | 0.57 | 2.55 | \begin{tabular}{l} \multicolumn{1}{c}{Continuous (every quarter cup, or 32.75 g/1000 kcal)} \end{tabular} |
| Person-years, n | 162,143 | 601,356 | 602,350 | 624,987 | \begin{tabular}{l} \multicolumn{1}{c}{Overall} \end{tabular} |
| Overall | 1,390 | 5,667 | 5,654 | 5,707 | \begin{tabular}{l} \multicolumn{1}{c}{Age-Adjusted HR (95% CI)} \end{tabular} |
| Age-Adjusted HR (95% CI)\(^3\) | 1 | 1.11 (1.05, 1.18) | 1.12 (1.06, 1.19) | 1.08 (1.02, 1.14) | \begin{tabular}{l} 0.41 \end{tabular} |
| Multivariable-Adjusted HR (95% CI)\(^4\) | 1 | 1.05 (0.99, 1.11) | 1.05 (0.99, 1.11) | 1.00 (0.95, 1.07) | \begin{tabular}{l} 0.04 \end{tabular} |
| Localized | 129 | 476 | 488 | 482 | \begin{tabular}{l} \multicolumn{1}{c}{Age-Adjusted HR (95% CI)} \end{tabular} |
| Age-Adjusted HR (95% CI)\(^3\) | 1 | 0.96 (0.79, 1.17) | 0.98 (0.81, 1.19) | 0.93 (0.77, 1.13) | \begin{tabular}{l} 0.44 \end{tabular} |
| Multivariable-Adjusted HR (95% CI)\(^4\) | 1 | 0.87 (0.72, 1.06) | 0.88 (0.72, 1.07) | 0.83 (0.68, 1.01) | \begin{tabular}{l} 0.18 \end{tabular} |
| Advanced | 146 | 618 | 629 | 637 | \begin{tabular}{l} \multicolumn{1}{c}{Age-Adjusted HR (95% CI)} \end{tabular} |
| Age-Adjusted HR (95% CI)\(^3\) | 1 | 1.15 (0.96, 1.38) | 1.18 (0.99, 1.42) | 1.14 (0.95, 1.37) | \begin{tabular}{l} 0.86 \end{tabular} |
| Multivariable-Adjusted HR (95% CI)\(^4\) | 1 | 1.11 (0.92, 1.33) | 1.13 (0.94, 1.36) | 1.09 (0.90, 1.30) | \begin{tabular}{l} 0.84 \end{tabular} |
| Fatal | 73 | 211 | 211 | 235 | \begin{tabular}{l} \multicolumn{1}{c}{Age-Adjusted HR (95% CI)} \end{tabular} |
| Age-Adjusted HR (95% CI)\(^3\) | 1 | 0.81 (0.62, 1.06) | 0.84 (0.65, 1.10) | 0.88 (0.68, 1.15) | \begin{tabular}{l} 0.68 \end{tabular} |
| Multivariable-Adjusted HR (95% CI)\(^4\) | 1 | 0.84 (0.64, 1.11) | 0.89 (0.68, 1.17) | 0.93 (0.71, 1.22) | \begin{tabular}{l} 0.50 \end{tabular} |

\(^1\) Intake density is based on gram per 1000 kcal. C, category.
\(^2\) Median was used to assess linear trend.
\(^3\) Age-adjusted model adjusted for age (years).
\(^4\) Multivariable model adjusted for age (continuous, years), BMI (continuous, kg/m\(^2\)), calories (continuous, kcal/day), education (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 vegetable, fruit, and alcohol intake (continuous).
TABLE 3 Hazard ratios and 95% confidence intervals for risk of prostate cancer associated with peanut butter intake (N=171,523)

| Peanut Butter Intake | C1 | C2 | C3 | C4 | P for trend | Continuous (every 1 tablespoon, or 16 g/1000 kcal) |
|----------------------|----|----|----|----|-------------|-----------------------------------------------|
| Median nut intake, g/1000 kcal | 0 | 0.15 | 0.78 | 3.71 |            |                                               |
| Person-years, n | 448,342 | 520,013 | 505,046 | 520,897 |            |                                               |
| Overall |             |            |            |            |             |                                               |
| Cases (n) | 4,055 | 4,842 | 4,703 | 4,850 |            |                                               |
| Age-Adjusted HR (95% CI) | 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 | 1.03 (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) | 357 | 415 | 407 | 401 |            |                                               |
| Age-Adjusted HR (95% CI) | 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 | 0.98 (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) | 431 | 551 | 500 | 555 |            |                                               |
| Age-Adjusted HR (95% CI) | 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 | 1.10 (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) | 158 | 187 | 182 | 205 |            |                                               |
| Age-Adjusted HR (95% CI) | 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 | 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) |

1 Intake density is based on gram per 1000 kcal. C, category.
2 Median was used to assess linear trend.
3 Age-adjusted model adjusted for age (years).
4 Multivariable model adjusted for age (continuous, years), BMI (continuous, kg/m²), calories (continuous, kcal/day), education (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 vegetable, fruit, and alcohol intake (continuous).
Table 4 Hazard ratios and 95% confidence intervals for risk of prostate cancer according to total nut intake¹

| Total Nut Intake | C1   | C2   | C3   | C4   | P for trend² |
|------------------|------|------|------|------|--------------|
| **Person-years, n** | 80,841 | 632,269 | 632,815 | 633,335 |              |
| **Overall**       |      |      |      |      |              |
| Cases (n)         | 700  | 5,920 | 5,861 | 5,840 |              |
| Age-Adjusted HR (95% CI)³ | 1.09 (1.01, 1.18) | 1.09 (1.00, 1.17) | 1.07 (0.99, 1.15) | 0.20 |
| Multivariable-Adjusted HR (95% CI)⁴ | 1.03 (0.96, 1.12) | 1.02 (0.95, 1.11) | 1.00 (0.93, 1.09) | 0.09 |
| **Localized**     |      |      |      |      |              |
| Cases (n)         | 71   | 506  | 508  | 486  |              |
| Age-Adjusted HR (95% CI)³ | 0.89 (0.70, 1.15) | 0.89 (0.70, 1.14) | 0.86 (0.67, 1.10) | 0.47 |
| Multivariable-Adjusted HR (95% CI)⁴ | 0.82 (0.64, 1.05) | 0.80 (0.62, 1.03) | 0.77 (0.60, 0.99) | 0.36 |
| **Advanced**      |      |      |      |      |              |
| Cases (n)         | 63   | 656  | 631  | 673  |              |
| Age-Adjusted HR (95% CI)³ | 1.34 (1.04, 1.74) | 1.30 (1.00, 1.68) | 1.36 (1.05, 1.76) | 0.59 |
| Multivariable-Adjusted HR (95% CI)⁴ | 1.26 (0.97, 1.63) | 1.21 (0.93, 1.57) | 1.27 (0.98, 1.65) | 0.64 |
| **Fatal**         |      |      |      |      |              |
| Cases (n)         | 29   | 222  | 239  | 236  |              |
| Age-Adjusted HR (95% CI)³ | 1.02 (0.69, 1.49) | 1.11 (0.75, 1.63) | 1.06 (0.72, 1.56) | 0.88 |
| Multivariable-Adjusted HR (95% CI)⁴ | 0.99 (0.67, 1.46) | 1.08 (0.73, 1.59) | 1.04 (0.70, 1.54) | 0.80 |

¹Intake density is based on gram per 1000 kcal. Q, quartile.
²Median was used to assess linear trend.
³Age-adjusted model adjusted for age (years).
⁴Multivariable model adjusted for age (years), BMI (kg/m²), calories (kcal/day), education, smoking status, physical activity, race, self-reported health, cardiovascular disease, marriage, prostate cancer screening, family history of prostate cancer and vegetable, fruit, and alcohol intake.
### Table 5 Hazard ratios and 95% confidence intervals for risk of prostate cancer associated with nut consumption frequency

| Frequency | Never to 1-6 times per year | 7-11 times per year to 1 time per month | 2-3 times per month to 1-2 times per week | 3-4 times per week to 2+ times per day | P for trend |
|-----------|-----------------------------|----------------------------------------|------------------------------------------|----------------------------------------|------------|
| Person-years, n | 608,146                     | 597,366                                | 615,392                                 | 184,167                                |            |
| Overall Prostate Cancer |                                        |                                        |                                        |                                        |            |
| Cases (n) | 5,483                       | 5,616                                  | 5,783                                   | 1,663                                  |            |
| Age-Adjusted HR (95% CI) \(^1\) | 1.06 (1.02, 1.10)            | 1.05 (1.01, 1.09)                      | 0.98 (0.93, 1.04)                      | 0.07                                  | 0.50       |
| Multivariable-Adjusted HR (95% CI) \(^2\) | 1.03 (0.99, 1.07)            | 1.00 (0.96, 1.04)                      | 0.93 (0.88, 0.98)                      |            |            |
| Localized Prostate Cancer |                                        |                                        |                                        |                                        |            |
| Cases (n) | 484                         | 470                                    | 481                                     | 148                                    |            |
| Age-Adjusted HR (95% CI) \(^1\) | 0.97 (0.86, 1.10)            | 0.97 (0.85, 1.10)                      | 1.00 (0.83, 1.20)                      | 0.80                                  | 0.80       |
| Multivariable-Adjusted HR (95% CI) \(^2\) | 0.93 (0.82, 1.06)            | 0.92 (0.81, 1.05)                      | 0.94 (0.78, 1.14)                      |            | 0.28       |
| Advanced |                                        |                                        |                                        |                                        |            |
| Cases (n) | 594                         | 562                                    | 649                                     | 181                                    |            |
| Age-Adjusted HR (95% CI) \(^1\) | 1.08 (0.96, 1.20)            | 1.08 (0.97, 1.21)                      | 0.98 (0.83, 1.16)                      | 0.58                                  | 0.58       |
| Multivariable-Adjusted HR (95% CI) \(^2\) | 1.05 (0.94, 1.18)            | 1.04 (0.93, 1.17)                      | 0.93 (0.78, 1.10)                      |            | 0.84       |
| Fatal |                                        |                                        |                                        |                                        |            |
| Cases (n) | 242                         | 205                                    | 211                                     | 77                                     |            |
| Age-Adjusted HR (95% CI) \(^1\) | 0.90 (0.75, 1.09)            | 0.88 (0.73, 1.06)                      | 1.00 (0.77, 1.29)                      | 0.46                                  | 0.46       |
| Multivariable-Adjusted HR (95% CI) \(^2\) | 0.92 (0.76, 1.11)            | 0.91 (0.75, 1.10)                      | 1.03 (0.79, 1.35)                      |            | 0.72       |

\(^1\) Age-adjusted model adjusted for age (years).

\(^2\) Multivariable model adjusted for age (years), BMI (kg/m\(^2\)), calories (kcal/day), education, smoking status, physical activity, race, self-reported health, cardiovascular disease, marriage, prostate cancer screening, family history of prostate cancer and vegetable, fruit, and alcohol intake.
SUPPLEMENTAL TABLE 1 Hazard ratios and 95% confidence intervals for risk of prostate cancer associated with nut and peanut butter consumption after exclusion of first 2 years of follow-up\(^1\)

| Nut Intake | Peanut Butter Intake |
|------------|----------------------|
| C1         | C2           | C3         | C4         | C1         | C2           | C3         | C4         |
| Person-years, n | 133,619 | 499,636 | 501,033 | 520,409 | 372,693 | 432,985 | 419,562 | 432,252 |
| Overall    | 1,222       | 5,029     | 5,060    | 5,090    | 3,597    | 4,299     | 4,182     | 4,354     |
| Cases (n)  | Age-Adjusted HR (95% CI)\(^2\) | 1 | 1.11 (1.05, 1.18) | 1.13 (1.06, 1.20) | 1.08 (1.02, 1.15) | 1 | 1.04 (1.00, 1.09) | 1.04 (0.99, 1.08) | 1.04 (0.99, 1.09) |
| Multivariable-Adjusted HR (95% CI)\(^3\) | 1 | 1.04 (0.98, 1.11) | 1.05 (0.99, 1.12) | 1.01 (0.94, 1.07) | 1 | 1.02 (0.98, 1.07) | 1.02 (0.98, 1.07) | 1.03 (0.99, 1.08) |
| Localized  | Cases (n)  | 129        | 476      | 488      | 482      | 357       | 415       | 407       | 401       |
| Age-Adjusted HR (95% CI)\(^2\) | 1 | 0.96 (0.79, 1.17) | 0.98 (0.81, 1.19) | 0.93 (0.77, 1.13) | 1 | 0.99 (0.86, 1.14) | 1.01 (0.88, 1.17) | 0.97 (0.84, 1.12) |
| Multivariable-Adjusted HR (95% CI)\(^3\) | 1 | 0.87 (0.72, 1.06) | 0.88 (0.72, 1.07) | 0.83 (0.68, 1.01) | 1 | 0.98 (0.85, 1.13) | 0.99 (0.86, 1.15) | 0.96 (0.83, 1.11) |
| Advanced   | Cases (n)  | 127        | 545      | 571      | 567      | 391       | 486       | 443       | 498       |
| Age-Adjusted HR (95% CI)\(^2\) | 1 | 1.16 (0.95, 1.40) | 1.22 (1.01, 1.48) | 1.16 (0.96, 1.40) | 1 | 1.09 (0.95, 1.24) | 1.01 (0.88, 1.16) | 1.09 (0.96, 1.25) |
| Multivariable-Adjusted HR (95% CI)\(^3\) | 1 | 1.11 (0.91, 1.34) | 1.16 (0.96, 1.41) | 1.09 (0.90, 1.33) | 1 | 1.07 (0.93, 1.22) | 1.00 (0.87, 1.15) | 1.08 (0.95, 1.24) |
| Fatal      | Cases (n)  | 59         | 164      | 183      | 194      | 132       | 151       | 151       | 169       |
| Age-Adjusted HR (95% CI)\(^2\) | 1 | 0.77 (0.57, 1.04) | 0.89 (0.67, 1.20) | 0.89 (0.67, 1.19) | 1 | 1.03 (0.81, 1.30) | 1.03 (0.82, 1.30) | 1.10 (0.87, 1.38) |
| Multivariable-Adjusted HR (95% CI)\(^3\) | 1 | 0.80 (0.59, 1.08) | 0.93 (0.69, 1.26) | 0.93 (0.69, 1.25) | 1 | 1.00 (0.79, 1.27) | 1.01 (0.80, 1.28) | 1.08 (0.85, 1.36) |

\(^1\) Intake density is based on gram per 1000 kcal. C, category.

\(^2\) Age-adjusted model adjusted for age (years).

\(^3\) Multivariable model adjusted for age (continuous, years), BMI (continuous, kg/m\(^2\)), calories (continuous, kcal/day), education (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 vegetable, fruit, and alcohol intake (continuous).