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Nut consumption and lung cancer risk: Results from two large observational studies

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Abstract

Background—Epidemiological evidence on the association between nut consumption and lung cancer risk is limited.

Methods—We investigated this relationship in the Environment And Genetics in Lung cancer Etiology (EAGLE) study, a population-based case-control study, and the National Institutes of Health (NIH) American Association of Retired Persons (AARP) Diet and Health Study, a prospective cohort. We identified 2098 lung cases for EAGLE and 18,533 incident cases in AARP. Diet was assessed by food frequency questionnaire for both studies. Multivariable odds ratios (ORs) and hazards ratio (HRs) and respective 95% confidence intervals (CIs) were calculated using unconditional logistic regression and Cox proportional hazards regression for EAGLE and AARP, respectively.

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Results—Higher frequency of intake of nut consumption was inversely associated with overall lung cancer risk (highest-versus-lowest quintile, OR_{EAGLE}=0.74, 95% CI=0.57–0.95; HR_{AARP}=0.86, 95% CI=0.81–0.91), regardless of smoking status. Results from the prospective cohort showed similar associations across histological subtypes, and a more pronounced benefits from nut consumption for those who smoked 1–20 cigarettes/day (OR_{EAGLE}=0.61, 95% CI=0.39–0.95; HR_{AARP}=0.83, 95% CI=0.74–0.94).

Conclusions—Nut consumption was inversely associated with lung cancer in two large population-based studies, and associations were independent of cigarette smoking and other known risk factors.

Impact—To our knowledge, this is the first study that examined the association between nut consumption and lung cancer risk by histologic subtypes and smoking intensity.

Keywords

Nut consumption; lung cancer risk; observational studies; epidemiology; cohort

Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide [1]. Cigarette smoking is the established primary risk factor for lung cancer. However, other factors, such as dietary intakes, may modify smoking-associated lung cancer risk [2].

Nut intake has been associated with lower risk of several chronic diseases, including cardiovascular disease [3, 4] and diabetes [5]. There is also a growing body of evidence suggesting that nut consumption may be associated inversely with cancer mortality [6–9] and incidence [10, 11]. To date, just a few studies have investigated associations between nut consumption and lung cancer and have observed evidence for an inverse association [12–14]. However, these studies had small sample sizes (n. cases range 178 to 342), and as such were unable to examine associations with lung cancer histological subtypes or examine associations separately in current, former, and never smokers. A recent prospective study (n. cases=9272) based on the National Institutes of Health (NIH) American Association of Retired Persons (AARP) Diet and Health Study [15] showed that several index-based dietary patterns, for which intake of nuts was a component but was not specifically examined in this study, were associated with modest reduction of lung cancer risk. The present study focuses on nut consumption and its relationship with lung cancer in this cohort.

Here, we investigated the association between nut consumption and lung cancer risk in the Environment And Genetics in Lung cancer Etiology (EAGLE), a population-based case-control study of over 2000 cases and 2000 controls [16], and further validated our findings in a large prospective cohort study, the AARP Diet and Health Study [17]. Our large sample size allowed us to explore the association with major lung cancer histology subtypes, and by stratification of smoking status.

Materials and Methods

Study population

The EAGLE Study is a large population-based case-control study conducted in the Lombardy region of Italy. Details of the study are previously described [16]. Between April 2002 and February 2005, primary lung cancer cases (n=2098) were identified from 13 hospitals, which covered approximately 80% of incident lung cancer cases in the catchment area, and consists of 216 municipalities, including five cities (Milan, Monza, Brescia, Pavia, and Varese) and surrounding towns and villages. Inclusion criteria for both cases and controls were Italian nationality between the ages of 35 and 79 years, official residents of the municipalities, and no severe disease that could impede participation. Case response rate was 86.6%. Approximately 95% of cases were confirmed pathologically or cytologically, and the remaining 5% were confirmed based on clinical history and imaging. Detailed histologic classification was recorded for all cases. Controls were randomly selected from the Lombardy Regional Health Service database, which contains demographic information for virtually all Italians from the catchment area, and were frequency-matched to cases based on sex, 5-year age group, and area of residence. Family physicians for the potential controls were asked to verify the absence of lung cancer history or any advanced diseases that would impede participation. At study completion, 2120 controls were enrolled with an overall participation rate of 72.4%.

The EAGLE analysis excluded 582 participants (380 cases and 202 controls) who did not complete the food frequency questionnaire (FFQ), resulting in a study population of 1721 cases and 1918 controls. The study protocol was approved by the Institutional Review Board of the US National Cancer Institute and the involved institutions in Italy. Informed consent was obtained for all subjects prior to study participation.

The AARP Diet and Health Study is a large prospective study of members of AARP, formally the American Association of Retired Persons, established in 1995 to 1996. Details of the study design have been previously described [17]. AARP members (n=617,119) aged 50 to 71 years and resided in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed a self-administered questionnaire where demographics, health-related behaviors, and diet were queried. The study cohort included 566,398 participants who satisfactorily completed the baseline questionnaire and provided informed consent. We excluded individuals with prevalent cancer except non-melanoma skin cancer (n=52,708), proxy respondents (n=14,398), those with missing information on nut consumption and with log-transformed total energy intake of more than two interquartile ranges from the median (n=3437), and individuals with zero years of follow-up (n=70); 495,785 individuals were included in our analysis. This study was approved by the Special Studies Institutional Review Board at the National Cancer Institute.

Incident lung cancer cases were identified through linkage with 11 state cancer registry databases which included the eight original and three additional states (Arizona, Texas, and Nevada) that a number of participants moved during follow-up [18]. Lung cancer cases were identified by anatomic site and histologic code of the *International Classification of Disease* *for Oncology* (ICD-O, third edition) [19]. As previously described, total lung cancer category included carcinoma of the bronchus and lung (ICD 34.0–34.9) [20]. Examined histological subtypes included adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma.

Exposure assessment

In EAGLE, tobacco exposure was categorized into active smoking (number of cigarettes per day averaged over a lifetime, age at initiation/quit, pack-years) and passive smoking (during childhood, at workplace, and at home during adulthood). Diet over the year prior to diagnosis for the cases and enrollment for the controls (cases were enrolled at diagnosis) was collected at baseline via a self-administered 58-item-FFQ specific to this Italian population. There was one question on total consumption of nuts (walnuts, hazelnuts, almonds, and peanuts), 41 on fruits and vegetables, nine on processed meats, one on pizza, and six on other meats and poultry. The FFQ queried frequency of consumption using 11 possible responses ("never" to "2 or more times per day") in the year prior to the study. Alcoholic beverage consumption was assessed using 3 possible response categories (yes, in the past, and never) in the year prior to the study, and 10 possible response categories ("never" to "6 or more times per day") for different age categories. Portion size was not queried.

At baseline, participants in the AARP cohort completed a 124-item-FFQ [21] that queried typical diet, including consumption of nuts (peanuts, walnuts, seeds, or other nuts) over the past year. The food items were constructed based on the method developed by Subar [22] with national dietary data from the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals [23]. Participants answered one question on their frequency of nut consumption using 10 categories, ranging from "never" to "2 or more times per day," and 3 categories for portion size.

Statistical analysis

In EAGLE, nut consumption was categorized by sex-specific quintiles based on distribution of frequency of consumption from the controls for each sex (Q1–Q5): Q1 (never), Q2 (1–6 times/year), Q3 (7–11 times/year), Q4 (1–3 times/month), and Q5 (1–5 times/week, and ≥1 time/day) during the past year. Frequency of nut consumption in AARP was categorized by quintiles based on distribution of frequency of consumption from the controls: Q1 (never), Q2 (1–6 times/year), Q3 (7–11 times/year), Q4 (1–3 time/month), and Q5 (1–6 times/week, and ≥1 time/day) during the past year.

The correlation between nut consumption and selected factors was examined by Pearson product-moment correlation coefficients. In EAGLE, odds ratios (ORs) and 95% confidence intervals (CIs) within sex-specific quintiles of nut consumption were obtained using logistic regression. In AARP, we used Cox proportional hazards regression [24] to estimate hazard ratios (HRs) and 95% CIs for nut consumption and total lung cancer, with non-consumers as the referent group and person-year as the underlying time metric. Person-years were calculated beginning on the date of questionnaire return until cancer diagnosis, movement out of the registry area, loss to follow-up, death, or the end of follow-up (December 31, 2011), whichever came first.

For EAGLE, models were adjusted for matching variables (age, sex, area of residence) and cumulative pack-years of cigarette smoking (continuous and 0 for never-smokers), and for AARP, age, sex, and cigarette smoking dose (categorical and 0 for never-smokers), but not residence. Both studies also adjusted for body mass index (BMI), education, cigarette smoking status, and years since last cigarette smoked for former-smokers (continuous in EAGLE, 0 for current-smokers and highest years for never-smokers; categorical in AARP, 0 for never-smokers, 1 for ≥10 years, 2 for 5–9 years, 3 for 1–4 years, 4 for within last year, and 5 for current-smokers). AARP additionally adjusted for energy intake. The analyses were further adjusted for selected dietary intakes (fruits, vegetables, red and processed meat, and alcohol), which have been hypothesized to be associated with lung cancer [25–27]. Variables for family history of lung cancer, previous lung diseases, and passive smoke exposures were not included in the final model since they did not substantially alter our results.

Subgroup analyses were conducted separately by smoking status (never, former, and current), smoking intensity (quintiles based on distribution of cigarettes per day in controls), sex, and major histologic subtypes (adenocarcinoma, squamous cell carcinoma, and small cell lung cancer). For sensitivity analyses, we conducted an analysis by tertiles of nut consumption. We further conducted lag-analyses, by 5 years, and 10 years in AARP.

Analyses in EAGLE were conducted using STATA 9.1 and in the AARP cohort using SAS 9.3 (SAS Institute, Cary, NC). For all comparisons, *p*-values were 2-sided and $\alpha<0.05$ indicated statistical significance.

Results

In EAGLE, cases (n=1721) and controls (n=1918) were similarly distributed by age, sex and BMI (Table 1). Compared with controls, cases were likely to be less educated, more likely to be current-smokers, and among ever-smokers, smoked more intensely. Cases had a lower average weekly consumption of nuts than controls. Overall, the proportion of participants was similarly distributed by smoking status across all categories of nut consumption in both cases and controls. In AARP (n=495,785), we identified 18,533 incident lung cancer cases during up to 16 years of follow-up (Table 2). A majority of lung cancer cases were diagnosed in current (38%) and former (52%) smokers at baseline. In general, cases ate more red meat and processed meat, less fruits and vegetables, and drank more alcohol in both EAGLE and AARP. Nut consumption was not correlated with any smoking-related factors, intakes of fruits and vegetables, red meat, processed meat, or lifetime alcohol consumption (Supplementary Table 1).

Table 3 presented results showing that individuals in the highest quintile of frequency of nut consumption had a 26% (OR_{EAGLE}=0.74, 95% CI=0.57–0.95, *p*-trend=0.017) and 14% (HR_{AARP}=0.86, 95% CI=0.81–0.91, *p*-trend<0.001) lower risk of developing lung cancer compared to those in the lowest quintile of intake. Similar inverse associations were observed in sex-stratified, analyses that examined tertiles of nut consumption (Supplementary Tables 2, 3, and 4), and in analyses excluding frequent (2 or more times a day) nut consumption. Across several lag-analyses in AARP, similar statistically significant inverse associations were observed (Supplementary Tables 5 and 6).

When stratified by smoking status (Table 3), significant inverse associations for nut consumption were observed for lung cancer cross all smoking status in AARP ($HR_{current}$=0.88, 95% CI=0.80–0.96, *p*-trend=0.004; HR_{former}=0.85, 95% CI=0.79–0.92, *p*-trend<0.001; HR_{never}=0.77, 95% CI=0.62–0.96, *p*-trend=0.02). Data from EAGLE showed significant inverse association for only current-smokers (OR_{EAGLE}=0.68, 95% CI=0.47–1.00, *p*-trend=0.05) with inverse associations that were not significant for former-smokers (OR_{EAGLE}=0.81, 95% CI=0.57–1.13, *p*-trend=0.213) and never-smokers (OR_{EAGLE}=0.91, 95% CI=0.43–1.90, *p*-trend=0.796), likely because of the small numbers in this category.

When we stratified by smoking intensity, the inverse associations were most pronounced among participants who smoked between 1–20 cigarettes/day among (OR_{EAGLE}=0.67, 95% CI=0.50–0.90, *p*-trend=0.008; HR_{AARP}=0.84, 95% CI=0.77–0.91, *p*-trend<0.001). Similar analyses within smoking-stratified categories showed that this more pronounced benefit from higher nut consumption was driven by the strong inverse associations observed for current smokers who smoked 1–20 cigarettes/day (Table 4). A sensitivity analysis excluding those with missing smoking information showed similar results.

We observed borderline or significant inverse associations in analyses stratified by histology subtypes (Table 5) in AARP ($HR_{adenocarcinoma}$=0.93, 95% CI=0.85–1.03, *p*-trend=0.151; $HR_{squamous}$=0.83, 95% CI=0.72–0.94, *p*-trend=0.004; and $HR_{small\text{-}cell}$ =0.76, 95% CI=0.65–0.90, *p*-trend=0.002). Conversely, probably due to smaller number of subjects across categories in EAGLE, we did not observe similar findings across histology groups in the case-control study.

Discussion

In the present study, we observed that higher frequent consumption of nuts was associated with a statistically significant (26% in EAGLE and 14% in AARP) reduced risk of lung cancer in both a large population-based case-control study from Northern Italy and in a large prospective cohort from the US, respectively. The inverse associations between nut consumption and lung cancer was independent of smoking characteristics. Moreover, lighter smokers (1–20 cigarettes per day) may benefit the most from higher consumption of nuts.

The body of evidence on nut consumption and lung cancer risk is scarce. Of the three published studies, two reported estimates and corresponding 95% CI on nut consumption and lung cancer risk [13, 14]; the remaining third did not report actual estimate but stated a non-significant inverse association was observed [12]. Of the two with reported estimates, the older hospital-based case-control study (n-cases=342) did not find an association ($OR_{\geq weekly+\text{-}versus\text{-}<weekly}$=1.15; 95% CI=0.66-2.02) [14]. Analyses from the Continuing Observation of Smoking Subjects (COSMOS) screening program (n-case=178) showed a non-significant inverse association ($OR_{Q4\text{-}VS\text{-}Q1}$=0.76; 95% CI=0.48–1.21) [13]. Both

studies had limited power to fully assess the relationship between nut consumption and lung cancer risk. Findings from the COSMOS suggested a stronger inverse association for increased consumption amongst the studied population of heavy smokers (smoking ≥1 pack/day). In the present study, when the analyses were restricted to participants who smoked ≥1 pack/year, we observed a non-significant 9% and a significant 10% reduction in lung cancer risk for EAGLE and AARP, respectively.

Although we observed evidence for an association among former and current smokers, associations appeared strongest among participants who smoked fewer than 20 cigarettes per day. A plausible explanation for this observation is that smokers may be exposed to free radicals and cellular damage from oxidative stress caused by cigarette smoke and the carcinogenic damage caused by high exposure among heavy smokers may overwhelm the potential protective effects derived from nut intake. More prospective studies are needed to confirm this finding in light smokers.

Our finding of an inverse association for nut intake for lung cancer risk might be explained by the bioactive constituents found in nuts. For example, tree nut extracts were found to be protective against oxidative damage [28], although results from animal studies and human clinical trials have shown mixed results [29, 30]. Studies on healthy male smokers consuming a diet enriched with powdered almonds showed a significant decrease in oxidative DNA damage and lipid peroxidation [31, 32]. This suggests nut consumption may decrease oxidative stress mediated by tobacco smoking [31].

Several other bioactive constituents of nuts may contribute to the associations observed here. Most nuts are high in n-3 polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acid (mainly oleic acid, which is more resistant to oxidation than PUFAs) known to have beneficial anti-inflammatory properties [4]. Recent studies have further linked inflammation to cellular mechanisms and to genomic pathways involved in carcinogenesis [33] with some epidemiologic evidence of a protective effect by dietary n-3 PUFAs (derived from fish/fish oil) on lung carcinogenesis [34, 35]. Nuts also provide a rich source of phytochemicals (polyphenols, phytoestrogens, and flavonoids), which are potent scavengers that may reduce oxidative stress and inhibit neutrophils respiratory burst to prevent carcinogenesis [36]. Previous studies have looked at polyphenols in relation to lung cancer risk in consumption of tea [37], and olive oil [14], and found mixed results. Higher intake of dietary flavonoids was associated with significantly reduced risk (17–76%) of lung cancer [38, 39], particularly among smokers [38], although some studies did not find an association [40, 41]. Antitumor activities by other components naturally found in nuts such as inositol [42], magnesium [43], and selenium [44] have also been evaluated, but findings are inconsistent. Emerging evidence suggests that phytochemicals and antioxidants may act synergistically to decrease oxidative damage [45].

Our study has several strengths, as it includes results from both a large population-based retrospective case-control study and a well-characterized prospective cohort. As the EAGLE study is more prone to bias due to its case-control study design, the similar results in a prospective cohort study validates and strengthen the inverse associations between nut consumption and lung cancer risk. It is the largest study to date, permitting analyses that were stratified by histologic subtypes, smoking status, and smoking intensity. Sensitivity analyses using lag showed persisted protective associations that further buttress the benefits observed for nut consumption and lung cancer.

Our study also has some limitations such as the possibility of recall bias due to the retrospective nature inherent in case-control study design in EAGLE. However, it is unlikely that our participants would consider nut eating to be a healthy choice, since the study was conducted in 2003–2005, when the potential health benefits of nut consumption were not widely hypothesized. Moreover, it is reassuring that we observed a similar association in our large prospective cohort. Since the FFQ queried about nut consumption at a single point, we lack data on the cumulative exposure of nut consumption. Furthermore, information on intake of individual type of nuts was not available for analyses. Nevertheless, studies that looked at differences between specific nuts [46, 47] suggested that consumption of a mixed type of nuts is important for a robust level of antioxidants. In addition, no validation study has been conducted to investigate the FFQ's ability to reflect nuts intake and thus this precluded the possibility to estimate measurement error. Nut consumption may be associated with aspects of a healthy lifestyle, such as lower exposures to tobacco and alcohol, lower BMI, lower intakes of red and processed meat, higher intakes of fruits and vegetables, and higher physical activity, but we observed no correlations between these factors and nut consumption. We adjusted for all important potential confounders in our analyses; nevertheless, we cannot exclude the possibility of residual confounding from smoking and dietary intake or additional unmeasured confounding that may affect our results. It is possible that changing smoking status could have a more profound effect such as that current-smokers may quit smoking during follow-up. Although we are unable to examine changing smoking status during follow-up, results from several lag analyses [by 5 years (for all smoking status and histologic subtypes) and 10 years (for current and former-smokers, and for squamous cell and small cell carcinoma)] in AARP showed that the inverse associations between nut consumption and lung cancer risk remained consistent (Supplementary Tables 5 and 6). In particular, the results for small cell carcinoma were persistent across lag-analyses, suggesting that nut consumption may be more protective in this group. Because small cell carcinoma is more associated with smoking-related lung cancer,, this observation may provide further evidence to support our hypothesis that smokers may benefit from higher nut consumption.

Altogether, the findings of the present study show that nut consumption is inversely related to all of the major histological subtypes of lung cancer. The results of this present study add to the emerging body of literature that investigates the potential protective effect of nut consumption on cancer risk and mortality, which may lead to evidence-based public health recommendations in the future. Further studies are needed to confirm these results in additional populations and to examine specific types of nuts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected baseline characteristics of the EAGLE study by lung cancer cases and controls of nut consumption[a]

			Quintile of total nut consumption (frequency per day) in controls[b]				
Characteristics	**Controls (n=1918)**	**Cases (n=1721)**	**1 (n=748)**	**2 (n=122)**	**3 (n=291)**	**4 (n=397)**	**5 (n=360)**
Sex, %							
Male	1387 (80.59)	1485 (77.42)	652 (87.17)	0 (0)	240 (82.47)	319 (80.45)	274 (76.11)
Age(years)[c]	65.49 (8.60)	66.31 (8.33)	66.96 (8.36)	64.10 (10.94)	63.78 (8.40)	64.92 (8.05)	64.93 (8.52)
BMI (kg/m^2)[c]	26.00 (3.85)	25.81 (4.18)	26.30 (4.11)	25.15 (4.07)	25.80 (3.49)	26.18 (3.76)	25.64 (3.50)
Education, n(%)							
Elementary	642 (38.12)	519 (27.07)	231 (30.97)	39 (31.97)	69 (23.71)	94 (23.68)	86 (23.89)
Middle school	484 (28.91)	555 (29.00)	209 (28.02)	37 (30.33)	103 (35.40)	103 (25.94)	103 (28.61)
≥High school	468 (27.44)	771 (40.22)	268 (35.92)	42 (34.43)	110 (37.80)	185 (46.60)	166 (46.11)
Smoking status, n(%)							
Never[d]	110 (6.33)	604 (31.52)	212 (28.42)	59 (48.36)	90 (30.93)	132 (33.25)	111 (30.83)
Former	761 (43.84)	838 (43.74)	344 (46.11)	29 (23.77)	128 (43.99)	171 (43.07)	166 (46.11)
Current	846 (48.73)	473 (24.69)	190 (25.47)	34 (27.87)	73 (25.09)	93 (23.43)	83 (23.06)
Cumulative pack-years of cigarette smoking (pack-year)[c]							
Ever	48.29 (27.45)	26.83 (21.37)	30.51 (23.41)	17.03 (16.69)	26.41 (20.52)	24.67 (19.74)	24.11 (18.64)
Former	43.54 (28.82)	22.62 (20.27)	25.92 (22.03)	6.87 (8.66)	23.33 (19.48)	20.13 (18.44)	20.53 (18.48)
Current	52.60 (25.41)	34.39 (21.22)	38.90 (23.59)	25.69 (17.08)	31.80 (21.30)	33.28 (19.23)	31.26 (16.92)
Smoking intensity (packs per day)[c,e]	0.79 (0.51)	1.12 (0.55)	0.86 (0.55)	0.51 (0.38)	0.79 (0.49)	0.76 (0.48)	0.73 (0.46)
Cigarettes smoking duration (years)[c,e]	31.78 (15.00)	42.91 (11.71)	33.54 (14.65)	28.48 (17.14)	31.76 (14.41)	30.30 (15.03)	30.57 (15.27)
Lifetime alcohol (g/week)[c]	162.51 (152.59)	203.71 (197.40)	172.15 (171.12)	71.35 (87.24)	169.44 (139.0)	158.90 (143.74)	171.88 (139.04)
Total red meat (servings/week)[c]	1.86 (1.59)	2.36 (1.99)	1.77 (1.60)	1.57 (1.37)	1.80 (1.51)	2.05 (1.54)	1.98 (1.73)

Characteristics	Controls (n=1918)	Cases (n=1721)	Quintile of total nut consumption (frequency per day) in controls[b] 1 (n=748)	2 (n=122)	3 (n=291)	4 (n=397)	5 (n=360)
Total processed meat consumption (servings/week)[c]	4.89 (3.87)	5.87 (4.86)	4.45 (3.87)	3.99 (3.52)	4.82 (3.65)	5.39 (3.89)	5.62 (3.98)
Total fruit and vegetables (servings/week)[c]	26.70 (12.76)	24.45 (12.82)	24.31 (12.40)	28.04 (13.39)	25.75 (12.38)	28.04 (12.38)	30.44 (12.89)
Total quercetin (servings/week)[c]	6.62 (4.68)	5.66 (4.42)	6.43 (4.85)	6.31 (4.60)	6.36 (4.38)	6.82 (4.56)	7.08 (4.65)
Total nut consumption (servings/week)[c]	0.68 (1.52)	0.55 (1.44)	0.04 (0.03)	0.07 (0.00)	0.17 (0.00)	0.41 (0.13)	2.90 (2.47)

Abbreviations: EAGLE, Environment And Genetics in Lung cancer Etiology; BMI, body mass index; SD, standard deviation.

[a] Some percentages do not sum to 100 due to missing data.

[b] Nut consumption in sex-specific quintiles based on distribution of controls for each sex: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day).

[c] Values are shown in mean (SD)

[d] Never-smokers of any tobacco products (cigarettes, pipes, cigars).

[e] Current-smokers and former-smokers.

Table 2

Selected baseline characteristics of the AARP Diet and Health Study by cohort and lung cancer cases of nut consumption[a]

			Quintile of total nut consumption (frequency per day) in cohort[b]				
Characteristics	**Cohort (n=495785)**	**Cases (n=18533)**	**1 (n=51217)**	**2 (n=122447)**	**3 (n=147636)**	**4 (n=87389)**	**5 (n=87096)**
Sex, n(%)							
Male	295953 (59.69)	11717 (63.22)	28459 (55.57)	66745 (54.51)	87902 (59.54)	55280 (63.26)	57567 (66.10)
Age (years)[c]	62.02 (5.37)	63.58 (4.86)	62.72 (5.30)	61.90 (5.40)	61.74 (5.38)	61.89 (5.36)	62.37 (5.31)
BMI (kg/m^2)[c]	27.11 (5.08)	26.57 (4.87)	27.18 (5.64)	27.37 (5.33)	27.30 (5.03)	27.10 (4.81)	26.41 (4.64)
Education, n(%)							
< High school	27854 (5.84)	1830 (9.87)	5446 (10.63)	8543 (6.98)	8098 (5.49)	4022 (4.60)	3575 (4.10)
Completed high school	145770 (29.40)	6253 (33.74)	18175 (35.49)	40701 (33.24)	43196 (29.25)	23156 (26.50)	20542 (23.58)
Post-high school training	110262 (23.10)	4663 (25.16)	10897 (21.28)	29370 (23.99)	34658 (23.48)	20296 (23.22)	19704 (22.62)
Completed college	185751 (38.92)	5140 (27.73)	14106 (27.54)	40098 (32.75)	57775 (39.13)	37726 (43.17)	41186 (47.29)
Smoking status, n(%)							
Never[d]	173887 (35.07)	1196 (6.45)	16489 (32.19)	41765 (34.11)	52250 (35.39)	31112 (35.60)	32271 (37.05)
Former	243703 (49.15)	9607 (51.84)	24228 (47.30)	60458 (49.37)	72592 (49.17)	43404 (49.67)	43021 (49.39)
Current	59353 (11.97)	7043 (38.00)	7603 (14.84)	15801 (12.90)	17391 (11.78)	9712 (11.11)	8846 (10.16)
Cigarettes smoked per day, n(%)[e]							
1–10	75002 (15.72)	2081 (11.23)	7659 (14.95)	19164 (15.65)	22928 (15.53)	13569 (15.53)	13763 (15.80)
11–20	93390 (19.57)	5378 (29.02)	10151 (19.82)	25265 (20.63)	29386 (19.90)	17114 (19.58)	16852 (19.35)
21–40	98133 (19.79)	6972 (37.62)	10539 (20.58)	24579 (20.07)	29119 (19.72)	17418 (19.93)	16478 (18.92)
>41	29072 (5.86)	2219 (11.97)	3482 (6.79)	7251 (5.92)	8550 (5.79)	5015 (5.74)	4774 (5.48)
Years since quitting smoking, n(%)[f]							
≥10	180197 (36.35)	5117 (27.61)	16342 (31.91)	43254 (35.32)	54231 (36.73)	32907 (37.66)	33463 (38.42)
5–9	34584 (6.98)	2139 (11.54)	4019 (7.85)	9465 (7.73)	10089 (6.83)	5725 (6.55)	5286 (6.07)
1–4	20074 (4.05)	1576 (8.50)	2707 (5.29)	5478 (4.47)	5697 (3.86)	3258 (3.73)	2934 (3.37)
0–1	8848 (1.78)	775 (4.18)	1160 (2.26)	2261 (1.85)	2575 (1.74)	1514 (1.73)	1338 (1.54)
Lifetime alcohol (g/week)[c]	12.67 (34.14)	18.64 (47.16)	10.06 (34.36)	10.79 (32.26)	12.34 (33.26)	13.89 (34.15)	16.19 (37.53)

			Quintile of total nut consumption (frequency per day) in cohort[b]				
Characteristics	**Cohort (n=495785)**	**Cases (n=18533)**	**1 (n=51217)**	**2 (n=122447)**	**3 (n=147636)**	**4 (n=87389)**	**5 (n=87096)**
Energy intake (calories/week)[c]	1851.81 (840.20)	1931.67 (916.68)	1719.07 (865.53)	1642.54 (754.49)	1792.58 (786.51)	1995.83 (832.03)	2179.96 (910.00)
Total red meat (g/week)[c]	66.28 (57.75)	75.57 (62.90)	56.95 (58.50)	56.61 (51.37)	66.16 (54.87)	76.16 (60.30)	75.64 (64.38)
Total processed meat (g/week)[c]	20.00 (23.00)	23.14 (24.94)	19.20 (25.57)	18.06 (22.31)	19.59 (22.13)	21.89 (22.63)	22.03 (23.88)
Total fruits (g/week)[c]	371.26 (343.66)	311.24 (308.95)	372.49 (384.26)	345.66 (333.00)	356.55 (328.32)	383.39 (334.45)	419.31 (361.77)
Total vegetables (g/week)[c]	300.49 (209.25)	288.02 (204.05)	293.01 (243.81)	269.93 (192.24)	288.67 (195.17)	320.04 (201.94)	248.29 (229.34)
Total nut consumption (g/week)[c]	20.14 (59.44)	19.64 (61.59)	0.00 (0.00)	1.75 (1.82)	7.08 (6.60)	17.80 (16.15)	82.34 (122.05)

Abbreviations: AARP, American Association of Retired Persons; BMI, body mass index; SD, standard deviation.

[a]Some percentages do not sum to 100 due to missing data.

[b]Nut consumption in sex-specific quintiles based on distribution of controls: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[c]Values are shown in mean (SD)

[d]Never-smokers of any tobacco products (cigarettes, pipes, cigars).

[e]Current-smokers and former-smokers.

[f]Former-smokers

Table 3

Odds ratios and Hazard ratios (95% Confidence Intervals) for lung cancer and nut consumption in EAGLE and AARP, by smoking status[a]

	Quintile of total nut consumption (frequency per day) in EAGLE						Quintile of total nut consumption (frequency per day) in AARP					
Nut consumption[b]	**1**	**2**	**3**	**4**	**5**	***p*-trend**	**1**	**2**	**3**	**4**	**5**	***p*-trend**
All participants												
Cases/controls	821/748	121/122	217/291	311/397	251/360		2484/48733	4834/117613	5270/142366	3053/84336	2892/84204	
Crude (95% CI)	1.00 (reference)	0.90 (0.69–1.18)	0.68 (0.56–0.83)	0.71 (0.60–0.85)	0.64 (0.53–0.77)	*<0.001*	1.00 (reference)	0.78 (0.74–0.82)	0.70 (0.67–0.73)	0.69 (0.65–0.72)	0.65 (0.62–0.69)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.92) (0.58–1.45	0.76 (0.59–0.99)	0.90 (0.71–1.14)	0.74 (0.57–0.95)	*0.017*	1.00 (reference)	0.93 (0.89–0.98)	0.89 (0.85–0.94)	0.89 (0.84–0.94)	0.86 (0.81–0.91)	*<0.001*
Current smokers												
Cases/controls	423/190	58/34	107/73	138/93	120/83		992/6611	1855/13946	2033/15358	1141/8571	1022/7824	
Crude (95% CI)	1.00 (reference)	0.77 (0.49–1.21)	0.66 (0.47–0.93)	0.67 (0.49–0.91)	0.65 (0.47–0.90)	*0.010*	1.00 (reference)	0.85 (0.79–0.92)	0.84 (0.78–0.90)	0.84 (0.78–0.92)	0.83 (0.76–0.90)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.91 (0.50–1.65)	0.74 (0.50–1.10)	0.70 (0.49–1.00)	0.68 (0.47–1.00)	*0.050*	1.00 (reference)	0.94 (0.87–1.02)	0.93 (0.86–1.01)	0.92 (0.85–1.01)	0.88 (0.80–0.96)	*0.004*
Former smokers												
Cases/controls	367/344	33/29	97/128	150/171	114/166		1233/22995	2560/57898	2661/69931	1583/41821	1570/41451	
Crude (95% CI)	1.00 (reference)	1.07 (0.63–1.79)	0.71 (0.53–0.96)	0.82 (0.63–1.07)	0.64 (0.49–0.85)	*0.002*	1.00 (reference)	0.79 (0.74–0.85)	0.68 (0.64–0.73)	0.68 (0.63–0.73)	0.68 (0.63–0.73)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.93 (0.45–1.91)	0.78 (0.55–1.11)	1.11 (0.81–1.52)	0.81 (0.57–1.13)	*0.213*	1.00 (reference)	0.93 (0.87–1.00)	0.85 (0.80–0.92)	0.86 (0.79–0.92)	0.85 (0.79–0.92)	*<0.001*
Never smokers												
Cases/controls	29/212	30/59	13/90	21/132	17/111		143/16346	262/41503	363/51887	212/30900	216/32055	
Crude (95% CI)	1.00 (reference)	3.72 (2.07–6.68)	1.06 (0.52–2.12)	1.16 (0.64–2.12)	1.12 (0.59–2.13)	*0.730*	1.00 (reference)	0.70 (0.57–0.86)	0.78 (0.64–0.94)	0.77 (0.62–0.95)	0.76 (0.61–0.93)	*0.010*
Multivariable[c] (95% CI)	1.00 (reference)	1.43 (0.71–2.89)	1.10 (0.51–2.36)	1.09 (0.56–2.11)	0.91 (0.43–1.90)	*0.796*	1.00 (reference)	0.75 (0.61–0.92)	0.84 (0.69–1.02)	0.80 (0.65–1.00)	0.77 (0.62–0.96)	*0.020*

Abbreviations: AARP, American Association of Retired Persons; EAGLE, Environment And Genetics in Lung cancer Etiology; OR, odds ratio; HR, hazards ratio; CI, confidence interval.

[a]Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

[b]Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); Nut consumption in sex-specific quintiles based on distribution of controls for AARP: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[c] Adjusted for age, sex, area of residence, education, body mass index, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never-smokers), years since last cigarette smoked (continuous, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; Adjusted for age, sex, education, body mass index, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never-smokers), years since last cigarette smoked (categorical, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.

Table 4

Odds ratios and Hazard ratios (95% Confidence Intervals) for lung cancer and nut consumption in EAGLE and AARP, by smoking intensity in ever smokers[a]

	Quintile of total nut consumption (frequency per day) in EAGLE						Quintile of total nut consumption (frequency per day) in AARP					
Nut consumption[b]	**1**	**2**	**3**	**4**	**5**	***p*-trend**	**1**	**2**	**3**	**4**	**5**	***p*-trend**
Ever smokers												
Smoked 1–20 cigarettes per day												
Cases/controls	517/422	72/61	140/166	188/222	158/211		1026/16784	2011/42418	2086/50228	1211/29472	1125/29490	
Crude (95% CI)	1.00 (reference)	0.96 (0.67–1.39)	0.69 (0.53–0.89)	0.69 (0.55–0.87)	0.61 (0.48–0.78)	*<0.001*	1.00 (reference)	0.75 (0.69–0.81)	0.65 (0.61–0.70)	0.65 (0.60–0.71)	0.61 (0.56–0.66)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.74 (0.45–1.22)	0.77 (0.57–1.04)	0.78 (0.60–1.03)	0.67 (0.50–0.90)	*0.008*	1.00 (reference)	0.92 (0.85–0.99)	0.85 (0.79–0.92)	0.86 (0.79–0.93)	0.84 (0.77–0.91)	*<0.001*
Smoked 21 or more cigarettes per day												
Cases/controls	273/112	19/2	64/35	100/43	76/38		1199/12822	2404/29426	2608/35061	1513/20920	1467/19785	
Crude (95% CI)	1.00 (reference)	3.90 (0.89–17.01)	0.75 (0.47–1.20)	0.95 (0.63–1.45)	0.82 (0.52–1.28)	*0.386*	1.00 (reference)	0.84 (0.78–0.90)	0.76 (0.71–0.81)	0.74 (0.69–0.80)	0.76 (0.70–0.82)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	3.72 (0.65–21.13)	0.70 (0.41–1.19)	1.13 (0.69–1.84)	0.91 (0.55–1.52)	*0.723*	1.00 (reference)	0.96 (0.89–1.03)	0.93 (0.86–0.99)	0.91 (0.84–0.98)	0.89 (0.82–0.97)	*0.003*
Current smokers												
Smoked 1–20 cigarettes per day												
Cases/controls	273/153	43/32	70/61	77/78	74/72		587/4343	1039/9300	1092/10181	616/5649	535/5003	
Crude (95% CI)	1.00 (reference)	0.79 (0.48–1.30)	0.67 (0.46–1.00)	0.61 (0.42–0.87)	0.62 (0.42–0.90)	*0.012*	1.00 (reference)	0.80 (0.72–0.88)	0.76 (0.69–0.84)	0.77 (0.69–0.86)	0.76 (0.68–0.86)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.81 (0.42–1.58)	0.80 (0.51–1.25)	0.61 (0.40–0.93)	0.61 (0.39–0.95)	*0.030*	1.00 (reference)	0.90 (0.81–1.00)	0.86 0.77–0.95)	0.85 (0.76–0.96)	0.83 (0.74–0.94)	*0.003*
Smoked 21 or more cigarettes per day												
Cases/controls	148/35	13/2	34/12	54/15	41/11		405/2268	816/4646	941/5177	525/2922	487/2821	
Crude (95% CI)	1.00 (reference)	1.54 (0.33–7.12)	0.67 (0.32–1.42)	0.85 (0.43–1.68)	0.88 (0.41–1.89)	*0.745*	1.00 (reference)	0.93 (0.82–1.04)	0.94 (0.83–1.05)	0.95 (0.84–1.08)	0.90 (0.79–1.03)	*0.117*
Multivariable[c] (95% CI)	1.00 (reference)	1.74 (0.23–12.96)	0.59 (0.26–1.39)	0.79 (0.36–1.72)	0.94 (0.40–2.24)	*0.897*	1.00 (reference)	1.01 (0.90–1.14)	1.05 (0.93–1.18)	1.04 (0.91–1.18)	0.94 (0.82–1.08)	*0.401*
Former smokers												
Smoked 1–20 cigarettes per day												

	Quintile of total nut consumption (frequency per day) in EAGLE						Quintile of total nut consumption (frequency per day) in AARP					
Nut consumption[b]	**1**	**2**	**3**	**4**	**5**	***p*-trend**	**1**	**2**	**3**	**4**	**5**	***p*-trend**
Cases/controls	242/267	27/29	67/105	104/143	79/139		439/12441	972/33118	994/40047	595/23823	590/24487	
Crude (95% CI)	1.00 (reference)	1.03 (0.59–1.78)	0.70 (0.49–1.00)	0.80 (0.59–1.09)	0.63 (0.45–0.87)	*0.005*	1.00 (reference)	0.80 (0.72–0.90)	0.67 (0.60–0.75)	0.68 (0.60–0.77)	0.66 (0.59–0.75)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.72 (0.33–1.54)	0.74 (0.48–1.12)	0.99 (0.68–1.43)	0.75 (0.50–1.12)	*0.162*	1.00 (reference)	0.94 (0.84–1.06)	0.84 (0.74–0.94)	0.86 (0.76–0.98)	0.84 (0.74–0.96)	*0.008*
Smoked 21 or more cigarettes per day												
Cases/controls	125/77	6/0	30/23	46/28	35/27		794/10554	1588/24780	1667/29884	988/17998	980/16964	
Crude (95% CI)	1.00 (reference)	NA	0.80 (0.44–1.48)	1.01 (0.58–1.75)	0.80 (0.45–1.42)	*0.445*	1.00 (reference)	0.82 (0.76–0.90)	0.71 (0.65–0.77)	0.70 (0.64–0.77)	0.73 (0.67–0.81)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	NA	0.79 (0.39–1.60)	1.46 (0.75–2.85)	0.95 (0.48–1.87)	*0.882*	1.00 (reference)	0.93 (0.85–1.01)	0.86 (0.79–0.94)	0.85 (0.77–0.94)	0.86 (0.78–0.95)	*0.002*

Abbreviations: AARP, American Association of Retired Persons; EAGLE, Environment And Genetics in Lung cancer Etiology; OR, odds ratio; HR, hazards ratio; CI, confidence interval; NA, not applicable.

[a] Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

[b] Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); Nut consumption in sex-specific quintiles based on distribution of controls for AARP: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[c] Adjusted for age, sex, area of residence, education, body mass index, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never-smokers), years since last cigarette smoked (continuous, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; Adjusted for age, sex, education, body mass index, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never-smokers), years since last cigarette smoked (categorical, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.

Table 5

Odds ratios and Hazard ratios (95% Confidence Intervals) for lung cancer and nut consumption in EAGLE and AARP, by histologic subtypes[a]

	Quintile of total nut consumption (frequency per day) in EAGLE						Quintile of total nut consumption (frequency per day) in AARP					
Nut consumption[b]	**1**	**2**	**3**	**4**	**5**	***p*-trend**	**1**	**2**	**3**	**4**	**5**	***p*-trend**
Adenocarcinoma												
Cases/controls	316/748	60/122	87/291	129/397	110/360		760/49023	1703/118080	1823/142904	1111/84631	1022/84503	
Crude (95% CI)	1.00 (reference)	1.16 (0.83–1.63)	0.71 (0.54–0.93)	0.77 (0.61–0.98)	0.72 (0.56–0.93)	*0.011*	1.00 reference	0.89 (0.82–0.97)	0.79 (0.72–0.85)	0.81 (0.74–0.89)	0.75 (0.68–0.82)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	0.89 (0.52–1.55)	0.71 (0.51–1.00)	0.87 (0.65–1.18)	0.79 (0.58–1.08)	*0.136*	1.00 reference	1.02 (0.93–1.11)	0.95 (0.87–1.04)	0.99 (0.90–1.09)	0.93 (0.85–1.03)	*0.151*
Squamous cell carcinoma												
Cases/controls	228/748	11/122	61/291	83/397	65/360		462/49023	734/118080	927/142904	505/84631	497/84503	
Crude (95% CI)	1.00 (reference)	0.30 (0.16–0.56)	0.69 (0.50–0.94)	0.69 (0.52–0.91)	0.59 (0.44–0.80)	*0.001*	1.00 (reference)	0.63 (0.57–0.71)	0.66 (0.59–0.73)	0.61 (0.54–0.69)	0.60 (0.53–0.68)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	1.08 (0.44–2.68)	0.81 (0.54–1.20)	0.96 (0.67–1.38)	0.74 (0.50–1.09)	*0.125*	1.00 (reference)	0.79 (0.70–0.89)	0.87 (0.78–0.98)	0.81 (0.71–0.93)	0.83 (0.72–0.94)	*0.004*
Small cell carcinoma												
Cases/controls	87/748	12/122	21/291	31/397	26/360		310/49023	578/118080	625/142904	344/84631	284/84503	
Crude (95% CI)	1.00 (reference)	0.85 (0.45–1.59)	0.62 (0.38–1.02)	0.67 (0.44–1.03)	0.62 (0.39–0.98)	*0.040*	1.00 (reference)	0.75 (0.65–0.86)	0.66 (0.58–0.76)	0.62 (0.53–0.72)	0.51 (0.44–0.60)	*<0.001*
Multivariable[c] (95% CI)	1.00 (reference)	1.41 (0.56–3.58)	0.91 (0.52–1.59)	0.89 (0.53–1.49)	0.96 (0.56–1.65)	*0.887*	1.00 (reference)	0.95 (0.83–1.10)	0.92 (0.80–1.06)	0.88 (0.75–1.03)	0.76 (0.65–0.90)	*0.002*

Abbreviations: AARP, American Association of Retired Persons; EAGLE, Environment And Genetics in Lung cancer Etiology; OR, odds ratio; HR, hazards ratio; CI, confidence interval.

[a] Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

[b] Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); Nut consumption in sex-specific quintiles based on distribution of controls for AARP: Quintile 1 (non-consumers), quintile 2 (1–6 times a year), quintile 3 (7–11 times a year), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[c] Adjusted for age, sex, area of residence, education, body mass index, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never-smokers), years since last cigarette smoked (continuous, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; Adjusted for age, sex, education, body mass index, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never-smokers), years since last cigarette smoked (categorical, 0 for never-smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.