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Research Article

Cancer Prevention Research

Mushroom Consumption and Risk of Total and Site-Specific Cancer in Two Large U.S. Prospective Cohorts

Dong Hoon Lee[1], Meng Yang[1], NaNa Keum[1,2], Edward L. Giovannucci[1,3,4], Qi Sun[1,4], and Jorge E. Chavarro[1,3,4]

Abstract

Several case–control studies have reported that mushroom consumption may be associated with reduced risk of certain cancers. However, epidemiologic studies have not yet prospectively examined the association of mushroom consumption with total and various site-specific cancer risks. This prospective cohort study included 68,327 women (Nurses' Health Study, 1986–2012) and 44,664 men (Health Professionals Follow-up Study, 1986–2012) who were free of cancer at baseline. Mushroom consumption was assessed at baseline using a validated food frequency questionnaire. Covariates were assessed using biennial questionnaires during the follow-up. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) of total and 17 site-specific cancers associated with mushroom consumption. During up to 26 years of follow-up, we documented 22,469 incident cancer cases (15,103 in women and 7,366 in men). In the pooled multivariable analysis, participants who consumed five or more servings of mushrooms per week had no significantly different risk of total cancer (HR, 1.06; 95% CI, 0.98–1.14) than participants who almost never consumed mushrooms. We consistently found no association between mushroom consumption and risk of 16 site-specific cancers. However, there was a marginal positive association between mushroom consumption and risk of lung cancer ($P_{trend} = 0.05$). In conclusion, we found no association between mushroom consumption and total and site-specific cancers in U.S. women and men. More prospective cohort studies are needed to examine the associations for specific cancer types in diverse racial/ethnic groups.

Introduction

Cancer is among the leading causes of death in both developed and developing countries and was responsible for an estimated 9.6 million deaths in 2018 (1). Moreover, cancer incidence and mortality rates are consistently increasing worldwide, posing an enormous global burden (2). Thus, cancer prevention has been a major target of research in public health. Studies have found that many cancers are attributable to preventable factors such as diet (3). The World Cancer Research Fund/American Institute of Cancer Research has reported that certain dietary factors or patterns have "convincing" or "probable" evidence to increase or decrease several types of cancers (4).

Mushrooms are generally known as a healthy food and are widely consumed in many countries. Mushrooms contain many important nutrients including riboflavin, niacin, vitamin D, fiber, selenium, potassium, and bioactive compounds (5). Laboratory studies have shown some evidence that mushrooms and mushroom extracts have anticarcinogenic and immunomodulating properties (6, 7). However, human studies evaluating the relation between mushroom intake and cancer risk are scarce. Several retrospective case–control studies have reported that high mushroom consumption may be associated with lower risk of breast cancer (8). Yet, retrospective case–control studies are prone to selection and recall biases, which are particularly problematic when addressing dietary exposures, and thus the observed association may have been overestimated. To date, only a few prospective cohort studies have examined the association of mushrooms, as a part of multiple food items, with certain cancer sites.

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [2]Department of Food Science and Biotechnology, Dongguk University, Goyang, South Korea. [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

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Corresponding Author: Jorge E. Chavarro, Harvard T.H. Chan School of Public Health, 665 Huntington Ave., Boston, MA 02115. Phone: 617-432-4584; Fax: 617-432-2435; E-mail: jchavarr@hsph.harvard.edu

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Moreover, the existing evidence is largely from relatively small studies from Asian countries. More prospective studies are warranted in diverse populations to better understand a role of mushroom consumption in the development of cancers. Therefore, we prospectively examined the association between mushroom consumption and risk of total and site-specific cancer in two large U.S. prospective cohorts of women and men.

Materials and Methods

Study population

The Nurses' Health Study (NHS) is an ongoing prospective cohort study which included 121,700 U.S. female nurses ages 30–55 years in 1976. The Health Professionals Follow-up Study (HPFS) is a parallel cohort study, which included 51,529 U.S. male health professionals ages 40–75 years in 1986. Participants were asked to complete a mailed questionnaire at enrollment and every 2 years thereafter to assess information on demographics, lifestyle factors, and medical history. Dietary data were assessed every 4 years using food frequency questionnaires (FFQ). The follow-up rates of two cohorts exceeded 90%.

In this study, we included participants who completed a FFQ in 1986. We excluded participants previously diagnosed with cancer (except for melanoma skin cancer) or had implausible calorie intake (<500 or ≥3,500 kcal/day for women; <800 or ≥4,200 kcal/day for men) at baseline. The final sample included 68,327 women and 44,664 men. This study was conducted in accordance with recognized ethical guidelines and approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health (Boston, MA). Informed written consent was obtained from all individual participants.

Mushroom consumption and covariate assessment

In 1986, participants reported how often on average they consumed mushrooms (fresh, cooked, or canned) during the past year among the following nine choices: never or less than once a month, 1–3 times a month, once a week, 2–4 times a week, 5–6 times a week, once a day, 2–3 times a day, 4–6 times a day, or more than 6 times a day. Other dietary data were collected as well using the same FFQs. The validity and reproducibility of FFQs have been described previously (9–12). Briefly, in a validation study, the deattenuated correlation comparing mushroom intake recorded in multiple prospectively collected diet records to mushroom intake reported in the FFQ was 0.65 and the average deattenuated correlation for all food items was 0.57 in men and 0.52 in women (11, 12). We characterized participants' diet into two major patterns defined as prudent and Western dietary patterns based on approximately 39 predefined food groups (excluding mushrooms) from FFQs via a principal component analysis (13). Other covariates including lifestyle and medical history were collected using biennial questionnaires over the follow-up.

Outcome assessment

Participants self-reported diagnoses of cancer and other diseases from biennial questionnaires. For participants who reported a cancer diagnosis, we obtained permission to acquire their medical records and pathologic reports. Study physicians, blinded to exposure status, reviewed medical records to confirm the cancer diagnosis and abstracted the information on histology, stage and anatomic location of the cancer. Confirmed cancers were defined according to the International Classification of Diseases, 9th revision. Deaths were identified through searching the National Death Index and reports from next-of-kin and postal authorities.

Statistical analysis

Person-years of the follow-up were accrued from the date of return of the 1986 baseline questionnaire to the date of diagnosis of cancer (excluding melanoma skin cancer), death, or the end of follow-up (June 2012 for the NHS; January 2012 for the HPFS), whichever came first. Mushroom consumption at baseline was categorized into five categories as follows: (i) never or less than once per month (almost never), (ii) less than once a week, (iii) once a week, (iv) 2–4 times a week, and (v) 5+ times a week. We also used mushroom consumption as a continuous variable (i.e., per two servings/week increase).

Cox proportional hazards regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of total and site-specific cancer associated with mushroom consumption. Age and calendar time were used as stratification variables. Multivariable models adjusted for race (white or non-white), height (continuous), body mass index (quintiles), family history of cancer (yes or no), physical exam in past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking in pack-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or ≥40), physical activity (quintiles), regular aspirin use (≥2 times/week; yes or no), multivitamin use (yes or no), total energy intake (quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥30 g/d), red and processed meat intake (quintiles), prudent dietary pattern (quintiles), and Western dietary pattern (quintiles). We additionally adjusted for prostate-specific antigen test in past 2 years (yes or no) for men and menopausal status (premenopause or postmenopause), postmenopausal hormone use (never, past, or current), and mammogram in past 2 years (yes or no) for women. All covariates were updated over the follow-up period. We tested for a linear trend of mushroom consumption by including mushroom consumption as a continuous variable in the models. Proportional hazards assumption was tested by including a cross-product term of mushroom consumption and time

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variable in the models ($P > 0.05$). Because we did not observe significant heterogeneity by sex, we pooled the data of women and men for cancers that are not sex-specific (i.e., postmenopausal, endometrial, and ovarian cancers for women and advanced prostate cancer for men). Finally, we conducted stratified analysis by smoking status to examine whether the association between mushroom consumption and risk of cancer differs by smoking status.

We used the SAS Software (version 9.4, SAS Institute) for all analyses. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant. Multiple comparison was adjusted using Bonferroni-corrected $P < 2.8 \times 10^{-3}$ (0.05 divided by 18 cancer outcomes; ref. 14).

Results

Participants who consumed more mushrooms had higher physical activity, multivitamin use, alcohol use, and overall diet quality (i.e., high prudent and low Western dietary patterns; Table 1). They also tended to have more frequent physical examinations, cancer screenings (i.e., physical examination, colonoscopy, sigmoidoscopy, or mammogram), and were less likely to be never smokers. The number of pack-years was lower among ever smokers who ate more mushrooms.

During up to 26 years of follow-up of 68,327 women and 44,664 men, we identified 15,103 and 7,366 cancers in women and men, respectively. In the pooled analyses of women and men, mushroom consumption was not related to risk of total cancer (Table 2). Compared with participants who almost never consumed mushrooms, those who consumed five or more servings of mushrooms per week had no significantly different risk of total cancer (HR, 1.06; 95% CI, 0.98–1.14). Increasing mushroom intake by two servings per week was not significantly associated with risk of total cancer (HR, 1.02; 95% CI, 0.97–1.07). When site-specific cancers were separately examined, we found no associations of mushroom consumption with risks of colorectal, lymphoma, bladder, pancreatic, kidney, leukemia, multiple myeloma, brain, oral, stomach, esophageal, and liver cancers. Sex-specific cancers including breast, endometrial, ovarian, and advanced prostate cancers were not associated with mushroom consumption either. However, there was a marginal positive association between mushroom consumption and risk of lung cancer (HR per two servings/week increase, 1.17; 95% CI, 1.00–1.36; $P_{trend} = 0.05$).

We then evaluated the relation of mushroom consumption and cancer risk within strata of smoking status (Table 3). In these analyses, we also found no association between mushroom consumption and total and most of site-specific cancers regardless of smoking status. However, we still observed a suggestive positive association between mushroom consumption and lung cancer risk in both ever smokers ($P_{trend} = 0.05$) and never smokers ($P_{trend} = 0.004$). These associations were not statistically significant after adjustment of multiple comparisons (Bonferroni-corrected $P < 0.0028$). Additional analyses stratified by other health behaviors including recency of physical examination, physical activity, and dietary patterns did not change the overall results.

When we stratified by sex, we observed no associations between mushroom consumption and total cancer risk in women (HR per two servings/week increase, 0.98; 95% CI, 0.93–1.04; Supplementary Table S1). Moreover, mushroom consumption was not associated with any site-specific cancers in women. In men, we found a marginal positive association of mushroom consumption with risk of total cancer (HR per two servings/week increase, 1.10; 95% CI, 1.00–1.21; $P_{trend} = 0.04$) and liver cancer (HR per two servings/week increase, 2.13; 95% CI, 1.12–4.05; $P_{trend} = 0.02$). These associations were not statistically significant after adjusting for multiple comparison (Supplementary Table S2). Other cancer sites were not associated with mushroom consumption in men.

Discussion

In the two large U.S. prospective cohorts, we found no association between mushroom consumption and total cancer risk. Moreover, mushroom consumption was not associated with 16 site-specific cancers including both major and relatively rare cancers. However, there was a marginal positive association between mushroom consumption and lung cancer risk, which persisted among participants who never smoked.

Although *in vitro* and animal studies have found the potential benefit of mushrooms on carcinogenesis (6, 7), few studies have evaluated this relation in humans. The existing epidemiologic evidence is largely from small retrospective case–control studies (<500 cases) that examined the association between mushroom consumption and risk of breast cancer. A dose-response meta-analysis of seven studies, including five case–control and two cohort studies, reported that increasing 1 g per day of mushrooms is associated with 3% decreased risk of breast cancer (RR, 0.97; 95% CI, 0.96–0.98) with moderate heterogeneity (I^2, 56.3%; $P = 0.015$; ref. 8). Because of small number of studies and lack of detailed information, this meta-analysis could not identify the source of heterogeneity.

Beside breast cancer, several studies have examined the association between mushroom consumption and risk of other cancer sites. Two small hospital-based case–control studies from Asia showed some evidence that high mushroom consumption may reduce stomach cancer risk (15, 16). A Korean study that examined the role of multiple dietary factors on stomach cancer found that participants with high mushroom consumption (>75th percentile) had 70% decreased risk of stomach cancer, compared with those with low mushroom consumption

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Table 1. Age standardized baseline characteristics of participants according to mushroom consumption in 1986

	Frequency of mushroom consumption, per serving				
Characteristics	**Never or almost never**	**<1/week**	**1/week**	**2–4/week**	**5+/week**
Women (NHS)					
No. of person	15,318	22,614	18,376	9,100	2,919
Age (years)	53.4 (7.2)	53.0 (7.2)	52.5 (7.1)	52.9 (7.0)	52.9 (6.8)
White (%)	97.2	97.7	98.3	98.0	98.1
Family history of cancer (%)	15.8	16.3	16.5	16.8	16.4
Height (cm)	163.6 (6.1)	163.8 (6.2)	163.9 (6.2)	164.0 (6.2)	164.4 (6.2)
Body mass index	25.3 (4.8)	25.2 (4.8)	25.4 (4.8)	25.5 (4.8)	25.3 (4.7)
Postmenopause (%)	54.9	54.2	54.9	54.2	54.1
Current hormone therapy use (%)	13.3	14.3	15.1	16.0	16.6
Physical examination in past 2 years (%)	64.8	66.2	67.1	68.5	69.5
History of colonoscopy or sigmoidoscopy (%)	16.8	17.8	18.7	18.7	20.5
Mammogram in past 2 years (%)[a]	71.8	75.7	77.2	78.6	80.5
Regular aspirin use (%)	40.1	40.0	42.0	41.9	40.4
Current use of multivitamin (%)	39.7	42.2	43.0	44.8	45.8
Physical activity (MET hour/week)	11.9 (19.1)	12.8 (18.6)	15.1 (21.6)	16.6 (21.2)	19.8 (25.9)
Never smoker (%)	49.4	45.0	41.1	40.6	37.4
No of pack-years among ever smokers	24.3 (19.1)	23.0 (19.1)	22.8 (18.9)	22.1 (18.8)	21.1 (18.2)
Calorie intake (kcal/day)	1,553 (505)	1,536 (488)	1,567 (483)	1,602 (483)	1,625 (501)
Alcohol intake (g/day)	4.2 (8.3)	6.0 (9.5)	7.4 (10.3)	8.1 (10.6)	9.6 (11.8)
Red and processed meat (no of servings/week)	7.0 (3.6)	6.8 (3.4)	6.9 (3.4)	6.9 (3.5)	6.5 (3.8)
Prudent pattern (highest quintile), %	9.2	13.2	23.0	39.2	51.4
Western pattern (highest quintile), %	22.3	19.1	19.8	19.5	17.5
Men (HPFS)					
No. of person	9,962	16,106	11,708	5,763	1,125
Age (years)	55.8 (10.0)	54.1 (9.8)	53.1 (9.5)	53.9 (9.7)	53.7 (9.5)
White (%)	89.5	89.8	90.7	90.5	89.5
Family history of cancer (%)	8.3	8.2	8.6	9.2	7.3
Height (cm)	178.1 (7.0)	178.1 (7.0)	178.1 (7.2)	178.1 (7.6)	178.7 (6.7)
Body mass index	25.4 (3.3)	25.5 (3.4)	25.6 (3.2)	25.7 (3.6)	25.8 (3.9)
Physical examination in past 2 years (%)[a]	56.9	58.8	60.8	59.3	62.8
History of colonoscopy or sigmoidoscopy (%)	24.0	25.9	26.7	27.9	28.5
Prostate specific antigen test in past 2 years (%)[a]	35.1	37.8	37.6	38.2	39.4
Regular aspirin use (%)	29.4	29.4	28.7	29.4	32.3
Current use of multivitamin (%)	40.5	41.2	41.8	43.5	44.6
Physical activity (MET hour/week)	18.7 (26.4)	20.0 (27.8)	22.0 (31.8)	23.7 (30.2)	29.0 (42.0)
Never smoker (%)	49.0	43.7	43.8	43.4	40.8
No of pack-years among ever smokers	26.3 (19.8)	25.4 (19.5)	25.0 (18.9)	25.0 (19.3)	23.1 (14.1)
Calorie intake (kcal/day)	1,906 (625)	1,921 (594)	2,036 (600)	2,157 (635)	2,298 (629)
Alcohol intake (g/day)	8.5 (14.2)	11.1 (15.1)	12.6 (15.8)	13.5 (16.2)	15.0 (18.0)
Red and processed meat (no of servings/week)	7.1 (5.4)	6.8 (5.0)	6.8 (4.9)	6.6 (5.2)	6.1 (5.2)
Prudent pattern (highest quintile), %	11.3	12.6	21.4	43.3	65.6
Western pattern (highest quintile), %	20.7	19.0	19.9	21.5	21.0

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population (except for age).
Abbreviation: MET, metabolic equivalent task.
[a]Data from 1988 for mammogram (women) and physical examination (men), and data from 1994 for prostate-specific antigen test (men) due to the first availability of the data.

(<25th percentile; RR, 0.30; 95% CI, 0.15–0.62; P_{trend} < 0.001; ref. 16). Similarly, a Japanese study showed an inverse, but marginally significant, association of specific type of mushrooms (*Hypsizygus marmoreus* and *Pholiota nameko*) with stomach cancer risk, particularly cardia cancer (15). Moreover, two large cohort studies of Chinese women and men in urban Shanghai investigated the role of dietary patterns and specific food groups on liver cancer risk (17). This study suggested that a vegetable-based dietary pattern was associated with reduced risk of liver cancer. Additional analyses of individual food groups showed that high consumption of mushrooms and several other foods (e.g., celery, allium and composite vegetables, and legumes and legume products) were associated with decreased risk of liver cancer. Compared with those in the lowest quartile, participants in the highest quartile of mushroom consumption had 34% lower risk of liver cancer (RR, 0.66; 95% CI, 0.46–0.95; $P_{trend} = 0.03$) after adjustment for dietary pattern. Unlike stomach and liver cancers, a couple of studies that examined other cancer sites found no association between mushroom consumption and cancers of colorectum (15) and prostate (18).

Overall findings of the previous studies were not consistent with our study which showed no evident association between mushroom consumption and risk of total and site-specific cancers. There are several potential reasons for why we see overall null results. First of all, compared with prospective cohort studies (19, 20), retrospective case–control studies (21–25) tended to show a significant or suggestive inverse association between mushroom

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Table 2. Mushroom consumption and risk of total and site-specific cancer (NHS, 1986–2012; HPFS, 1986–2012)

	Frequency of mushroom consumption, per serving						
	Never or almost never	<1/week	1/week	2–4/week	5+/week	Per 2/week increase	P_{trend}
Total cancer (n = 22,469)[a,b]							
Event	4,981	7,688	5,938	3,009	853		
Person-years	516,441	803,462	631,961	310,373	8,4651		
Age-adjusted HR (95% CI)	1 (ref)	1.04 (1.01–1.08)	1.05 (1.01–1.09)	1.06 (1.01–1.11)	1.08 (1.00–1.16)	1.03 (0.98–1.08)	0.21
Multivariable HR (95% CI)	1 (ref)	1.03 (1.00–1.07)	1.04 (1.00–1.08)	1.04 (0.99–1.09)	1.06 (0.98–1.14)	1.02 (0.97–1.07)	0.55
Cancer sites[b]							
Colorectal cancer (n = 2,342)							
Event	553	793	647	281	68		
Age-adjusted HR (95% CI)	1 (ref)	0.98 (0.88–1.10)	1.08 (0.96–1.21)	0.92 (0.79–1.06)	0.87 (0.67–1.12)	0.90 (0.75–1.07)	0.24
Multivariable HR (95% CI)	1 (ref)	0.97 (0.87–1.09)	1.06 (0.94–1.19)	0.89 (0.76–1.04)	0.85 (0.65–1.10)	0.88 (0.73–1.06)	0.17
Lung cancer (n = 2,036)							
Event	414	761	521	264	76		
Age-adjusted HR (95% CI)	1 (ref)	1.26 (1.12–1.43)	1.15 (1.01–1.31)	1.16 (1.00–1.36)	1.25 (0.98–1.60)	1.09 (0.94–1.27)	0.25
Multivariable HR (95% CI)	1 (ref)	1.25 (1.11–1.42)	1.19 (1.04–1.37)	1.26 (1.07–1.48)	1.36 (1.05–1.76)	1.17 (1.00–1.36)	0.05
Lymphoma (n = 1,456)							
Event	306	518	369	207	56		
Age-adjusted HR (95% CI)	1 (ref)	1.13 (0.98–1.30)	1.06 (0.91–1.23)	1.18 (0.99–1.41)	1.23 (0.92–1.64)	1.12 (0.94–1.33)	0.19
Multivariable HR (95% CI)	1 (ref)	1.12 (0.97–1.30)	1.06 (0.91–1.25)	1.20 (1.00–1.45)	1.25 (0.93–1.69)	1.13 (0.95–1.35)	0.18
Bladder cancer (n = 1,001)							
Event	214	368	258	128	33		
Age-adjusted HR (95% CI)	1 (ref)	1.18 (0.99–1.40)	1.13 (0.94–1.36)	1.11 (0.89–1.38)	1.24 (0.85–1.79)	1.15 (0.91–1.44)	0.25
Multivariable HR (95% CI)	1 (ref)	1.14 (0.96–1.35)	1.13 (0.93–1.37)	1.14 (0.90–1.44)	1.29 (0.88–1.89)	1.18 (0.94–1.49)	0.15
Pancreatic cancer (n = 561)							
Event	124	211	136	77	13		
Age-adjusted HR (95% CI)	1 (ref)	1.14 (0.91–1.43)	1.01 (0.79–1.29)	1.15 (0.86–1.53)	0.80 (0.45–1.42)	0.94 (0.66–1.35)	0.76
Multivariable HR (95% CI)	1 (ref)	1.14 (0.91–1.43)	0.99 (0.77–1.28)	1.10 (0.81–1.49)	0.76 (0.42–1.38)	0.90 (0.61–1.33)	0.61
Kidney cancer (n = 545)[d]							
Event	128	184	146	76	11		
Age-adjusted HR (95% CI)	1 (ref)	0.91 (0.73–1.14)	0.98 (0.77–1.24)	0.99 (0.74–1.31)	0.56 (0.30–1.05)	0.77 (0.51–1.17)	0.22
Multivariable HR (95% CI)	1 (ref)	0.94 (0.75–1.19)	1.05 (0.82–1.35)	1.10 (0.81–1.49)	0.66 (0.35–1.24)	0.89 (0.58–1.35)	0.57
Leukemia (n = 386)							
Event	93	151	84	43	15		
Age-adjusted HR (95% CI)	1 (ref)	1.09 (0.84–1.42)	0.82 (0.60–1.10)	0.86 (0.60–1.25)	1.26 (0.73–2.20)	0.88 (0.54–1.41)	0.59
Multivariable HR (95% CI)	1 (ref)	1.07 (0.82–1.40)	0.79 (0.58–1.07)	0.82 (0.56–1.21)	1.15 (0.65–2.05)	0.83 (0.49–1.38)	0.47
Multiple myeloma (n = 334)							
Event	77	104	100	43	10		
Age-adjusted HR (95% CI)	1 (ref)	0.91 (0.68–1.23)	1.17 (0.87–1.58)	1.01 (0.69–1.47)	0.93 (0.48–1.81)	0.90 (0.56–1.44)	0.66
Multivariable HR (95% CI)	1 (ref)	0.92 (0.68–1.25)	1.21 (0.88–1.65)	1.07 (0.72–1.59)	1.01 (0.51–2.01)	0.93 (0.58–1.49)	0.76
Brain cancer (n = 270)							
Event	61	89	72	36	12		
Age-adjusted HR (95% CI)	1 (ref)	1.00 (0.72–1.39)	1.05 (0.74–1.48)	1.01 (0.67–1.54)	1.41 (0.75–2.64)	1.36 (0.96–1.94)	0.09
Multivariable HR (95% CI)	1 (ref)	1.03 (0.74–1.44)	1.07 (0.74–1.53)	1.03 (0.66–1.60)	1.43 (0.74–2.75)	1.37 (0.95–1.97)	0.09
Oral cancer (n = 214)							
Event	52	74	50	33	5		
Age-adjusted HR (95% CI)	1 (ref)	0.94 (0.65–1.34)	0.83 (0.56–1.24)	1.13 (0.73–1.76)	0.65 (0.25–1.65)	0.84 (0.44–1.62)	0.61
Multivariable HR (95% CI)	1 (ref)	0.93 (0.64–1.34)	0.83 (0.55–1.25)	1.17 (0.73–1.88)	0.68 (0.26–1.79)	0.88 (0.45–1.71)	0.71
Stomach cancer (n = 203)							
Event	46	72	55	22	8		
Age-adjusted HR (95% CI)	1 (ref)	1.10 (0.75–1.60)	1.14 (0.76–1.69)	0.91 (0.54–1.52)	1.30 (0.61–2.78)	0.99 (0.58–1.69)	0.97
Multivariable HR (95% CI)	1 (ref)	1.12 (0.76–1.64)	1.16 (0.77–1.77)	0.96 (0.56–1.64)	1.37 (0.62–3.02)	1.00 (0.59–1.68)	0.99
Esophageal (n = 199)							
Event	53	65	43	34	4		
Age-adjusted HR (95% CI)	1 (ref)	0.81 (0.56–1.18)	0.75 (0.50–1.14)	1.18 (0.76–1.83)	0.65 (0.23–1.82)	0.97 (0.52–1.83)	0.93
Multivariable HR (95% CI)	1 (ref)	0.74 (0.51–1.08)	0.69 (0.45–1.06)	1.09 (0.68–1.73)	0.57 (0.20–1.64)	0.90 (0.45–1.80)	0.77
Liver cancer (n = 113)							
Event	22	32	36	17	6		
Age-adjusted HR (95% CI)	1 (ref)	0.95 (0.55–1.65)	1.58 (0.92–2.71)	1.44 (0.76–2.74)	2.14 (0.85–5.34)	1.54 (0.96–2.46)	0.07
Multivariable HR (95% CI)	1 (ref)	1.05 (0.60–1.84)	1.85 (1.05–3.25)	1.67 (0.84–3.33)	2.40 (0.91–6.33)	1.66 (0.99–2.77)	0.05
Sex-specific cancer sites[c]							
Breast cancer (n = 5,397)							
Event	1,148	1,818	1,466	753	212		
Age-adjusted HR (95% CI)	1 (ref)	1.08 (1.00–1.16)	1.07 (0.99–1.15)	1.11 (1.01–1.22)	0.98 (0.84–1.13)	1.00 (0.91–1.09)	0.93
Multivariable HR (95% CI)	1 (ref)	1.04 (0.96–1.12)	1.01 (0.93–1.09)	1.03 (0.93–1.13)	0.89 (0.77–1.04)	0.93 (0.84–1.03)	0.19
Endometrial cancer (n = 1,065)							
Event	242	331	297	133	62		
Age-adjusted HR (95% CI)	1 (ref)	0.92 (0.78–1.09)	1.02 (0.86–1.21)	0.92 (0.74–1.14)	1.32 (1.00–1.75)	1.12 (0.93–1.36)	0.22
Multivariable HR (95% CI)	1 (ref)	0.91 (0.77–1.08)	0.98 (0.82–1.17)	0.83 (0.66–1.04)	1.16 (0.86–1.56)	1.03 (0.84–1.26)	0.77

(Continued on the following page)

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Table 2. Mushroom consumption and risk of total and site-specific cancer (NHS, 1986–2012; HPFS, 1986–2012) (Cont'd)

	Frequency of mushroom consumption, per serving						
	Never or almost never	<1/week	1/week	2–4/week	5+/week	Per 2/week increase	P_{trend}
Ovarian cancer ($n = 550$)							
Event	140	178	138	73	21		
Age-adjusted HR (95% CI)	1 (ref)	0.86 (0.69–1.07)	0.83 (0.65–1.05)	0.90 (0.68–1.20)	0.81 (0.51–1.29)	0.85 (0.60–1.21)	0.36
Multivariable HR (95% CI)	1 (ref)	0.83 (0.66–1.04)	0.83 (0.65–1.06)	0.95 (0.70–1.28)	0.87 (0.54–1.40)	0.92 (0.65–1.31)	0.66
Advanced prostate cancer ($n = 956$)							
Event	228	342	244	117	25		
Age-adjusted HR (95% CI)	1 (ref)	1.07 (0.90–1.27)	1.15 (0.96–1.38)	1.04 (0.83–1.30)	1.10 (0.72–1.66)	1.05 (0.81–1.36)	0.72
Multivariable HR (95% CI)	1 (ref)	1.07 (0.90–1.27)	1.15 (0.95–1.39)	1.01 (0.80–1.29)	1.06 (0.69–1.63)	1.02 (0.77–1.35)	0.89

NOTE: Age-adjusted models included age (months).

Multivariable models included for age, race (white or non-white), height (continuous), body mass index (quintiles), family history of cancer (yes or no), physical exam in past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking in pack-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or ≥40), physical activity (quintiles), regular aspirin use (yes or no), multivitamin use (yes or no), total energy intake (quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥30 g/d), red and processed meat intake (quintiles), prudent diet pattern (quintiles) and Western diet pattern (quintiles); prostate-specific antigen test in past 2 years (yes or no) for men only; and menopause status (premenopause or postmenopause), postmenopausal hormone use (never, past, or current), and mammogram in past 2 years (yes or no) for women only.

[a]Included only aggressive prostate cancer as total cancer.

[b]Pooled results of women and men.

[c]Sex-specific results of women (breast, endometrial, and ovarian cancers) and men (advanced prostate cancer).

consumption and breast cancer risk. Of note, other types of cancer did not have sufficient number of studies to compare between study design. Case–control studies are prone to recall bias, meaning that patients with cancer may underreport their mushroom consumption knowing that mushrooms are generally considered as a healthy food (26). In this case, high intake of mushrooms would appear to be beneficial to reduce cancer risk. Moreover, selection bias in retrospective case–control studies, especially hospital-based, is another source of bias that may affect the results (27). Second, the majority of case–control studies were from Asian countries including Korea, China, and Japan (15, 16, 21–25). In contrast, only a few studies were done in non-Asian populations in Europe and they were mostly cohort studies (18–20). In Asian countries, mushrooms are more commonly consumed and various types of edible mushrooms, including medicinal mushrooms, are widely available. In fact, Asian studies generally had higher average and larger variation in mushroom consumption compared with non-Asian studies. If a dose-response relationship exists, the true association may have been masked in populations with limited range of mushroom consumption (28). Moreover, most studies, including our study, did not have detailed information on types of mushrooms, thus we are examining the combined association of all edible mushrooms on cancer risk. Cultural differences related to types of mushrooms may affect the association, whether different types of mushrooms have different effects on cancer development. Given the growing interests in medicinal mushrooms, further epidemiologic studies and trials are needed to discover the potential anticancer effect of certain types of mushrooms.

While we observed no relation with total cancer and with most of the sites examined, we did observe a positive relation with lung cancer that was stronger among never smokers, as well as a positive association with liver cancer restricted to men. It is important to consider the possibility that these results may represent chance findings. Previous cohort studies that reported a suggestive inverse association between mushrooms and risk of a certain cancer may have had multiple testing issues (14). Interestingly, all cohort studies we found had examined various diets in relation to cancer risk and thus among many food items, mushrooms may have shown to be statistically significant by chance (17–20). Similarly, although our study examined one primary exposure (mushrooms), we had multiple outcomes (total and 17 cancer sites). Therefore, the observed positive associations of mushrooms with risk of lung (pooled data only) and liver (men data only) cancers could be due to chance, especially when considering the lack of convincing a priori hypothesis for these two sites. Moreover, when multiple comparisons were accounted for, mushroom consumption was not associated with any cancer sites.

Our study has considerable strengths. To our knowledge, this is the first and the largest prospective study to examine the association between mushroom consumption and cancer risk. During 26 years of follow-up, we collected sufficient number of cancer cases, which allowed us to examine most major cancers and some rare cancers (17 cancer sites). We had detailed and repeated information on lifestyle factors and medical history over the follow-up to finely control for potential confounders. There are several limitations as well. First, mushroom consumption was assessed only once at baseline using FFQ. Thus, single measure may not reflect the long-term mushroom consumption but the measurement error is likely to be nondifferential, which yields more conservative results. Second, detailed information on types of mushrooms were not reported. Some types of mushrooms (e.g., medicinal mushrooms) may have different effect on cancer risk. Third, our cohorts consisted of White health professionals,

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Table 3. Mushroom consumption and risk of total and site-specific cancer by smoking status (NHS, 1986–2012; HPFS, 1986–2012)

	Frequency of mushroom consumption, per serving						
	Never or almost never	<1/week	1/week	2–4/week	5+/week	Per 2/week increase	P_{trend}
Total cancer[a,b]							
Ever smokers (n = 13,365)	1 (ref)	1.03 (1.00–1.07)	1.04 (1.00–1.08)	1.04 (0.99–1.09)	1.06 (0.98–1.14)	1.02 (0.97–1.07)	0.54
Never smokers (n = 9,104)	1 (ref)	1.04 (1.00–1.08)	1.05 (1.01–1.09)	1.06 (1.01–1.11)	1.08 (1.00–1.16)	1.03 (0.98–1.08)	0.28
Cancer sites[b]							
Colorectal cancer							
Ever smokers (n = 1,376)	1 (ref)	0.97 (0.87–1.09)	1.06 (0.94–1.19)	0.89 (0.76–1.04)	0.85 (0.65–1.10)	0.88 (0.73–1.06)	0.17
Never smokers (n = 966)	1 (ref)	0.98 (0.87–1.09)	1.06 (0.94–1.20)	0.90 (0.77–1.05)	0.86 (0.66–1.12)	0.89 (0.74–1.07)	0.21
Lung cancer							
Ever smokers (n = 1,732)	1 (ref)	1.25 (1.11–1.42)	1.19 (1.04–1.37)	1.26 (1.07–1.48)	1.36 (1.05–1.76)	1.17 (1.00–1.36)	0.05
Never smokers (n = 304)	1 (ref)	1.29 (1.14–1.46)	1.28 (1.11–1.46)	1.37 (1.16–1.62)	1.56 (1.21–2.02)	1.24 (1.07–1.42)	0.004
Lymphoma							
Ever smokers (n = 762)	1 (ref)	1.12 (0.97–1.30)	1.06 (0.91–1.25)	1.20 (0.99–1.45)	1.25 (0.93–1.68)	1.13 (0.94–1.34)	0.19
Never smokers (n = 694)	1 (ref)	1.12 (0.97–1.30)	1.07 (0.91–1.25)	1.20 (1.00–1.45)	1.26 (0.93–1.69)	1.13 (0.95–1.35)	0.18
Bladder cancer							
Ever smokers (n = 682)	1 (ref)	1.14 (0.96–1.35)	1.13 (0.93–1.37)	1.14 (0.90–1.44)	1.29 (0.88–1.89)	1.18 (0.94–1.49)	0.15
Never smokers (n = 319)	1 (ref)	1.15 (0.97–1.37)	1.16 (0.96–1.40)	1.18 (0.93–1.49)	1.37 (0.93–2.01)	1.23 (0.98–1.54)	0.08
Pancreatic cancer							
Ever smokers (n = 328)	1 (ref)	1.14 (0.91–1.43)	0.99 (0.76–1.28)	1.10 (0.81–1.49)	0.76 (0.42–1.37)	0.90 (0.61–1.33)	0.61
Never smokers (n = 233)	1 (ref)	1.14 (0.90–1.43)	0.99 (0.77–1.28)	1.10 (0.81–1.49)	0.77 (0.43–1.39)	0.91 (0.62–1.34)	0.64
Kidney cancer							
Ever smokers (n = 299)	1 (ref)	0.94 (0.75–1.19)	1.05 (0.82–1.35)	1.10 (0.81–1.49)	0.66 (0.35–1.24)	0.89 (0.58–1.35)	0.57
Never smokers (n = 246)	1 (ref)	0.95 (0.75–1.19)	1.06 (0.83–1.36)	1.12 (0.82–1.51)	0.67 (0.36–1.26)	0.90 (0.60–1.37)	0.63
Leukemia							
Ever smokers (n = 215)	1 (ref)	1.07 (0.82–1.40)	0.79 (0.58–1.07)	0.82 (0.56–1.21)	1.15 (0.65–2.04)	0.83 (0.49–1.38)	0.47
Never smokers (n = 171)	1 (ref)	1.07 (0.82–1.40)	0.78 (0.57–1.07)	0.82 (0.56–1.21)	1.16 (0.65–2.06)	0.83 (0.50–1.39)	0.48
Multiple myeloma							
Ever smokers (n = 185)	1 (ref)	0.92 (0.68–1.25)	1.21 (0.88–1.66)	1.07 (0.72–1.59)	1.03 (0.52–2.05)	0.94 (0.59–1.50)	0.79
Never smokers (n = 149)	1 (ref)	0.92 (0.68–1.25)	1.21 (0.88–1.66)	1.07 (0.72–1.59)	1.03 (0.52–2.04)	0.94 (0.58–1.50)	0.78
Brain cancer							
Ever smokers (n = 139)	1 (ref)	1.03 (0.74–1.44)	1.08 (0.75–1.54)	1.03 (0.66–1.60)	1.44 (0.75–2.78)	1.37 (0.96–1.97)	0.09
Never smokers (n = 131)	1 (ref)	1.03 (0.74–1.44)	1.07 (0.75–1.54)	1.03 (0.66–1.59)	1.45 (0.75–2.78)	1.36 (0.95–1.95)	0.09
Oral cancer							
Ever smokers (n = 132)	1 (ref)	0.93 (0.64–1.34)	0.83 (0.55–1.25)	1.18 (0.73–1.89)	0.68 (0.26–1.79)	0.88 (0.46–1.71)	0.71
Never smokers (n = 82)	1 (ref)	0.93 (0.64–1.33)	0.84 (0.56–1.27)	1.18 (0.74–1.89)	0.69 (0.26–1.82)	0.90 (0.46–1.75)	0.76
Stomach cancer							
Ever smokers (n = 115)	1 (ref)	1.12 (0.76–1.64)	1.16 (0.77–1.77)	0.96 (0.56–1.64)	1.37 (0.62–3.01)	1.00 (0.59–1.68)	0.99
Never smokers (n = 88)	1 (ref)	1.13 (0.77–1.66)	1.18 (0.78–1.79)	0.97 (0.57–1.67)	1.40 (0.64–3.10)	1.02 (0.60–1.72)	0.94
Esophageal							
Ever smokers (n = 145)	1 (ref)	0.74 (0.51–1.08)	0.69 (0.45–1.06)	1.09 (0.68–1.73)	0.57 (0.20–1.64)	0.90 (0.45–1.80)	0.77
Never smokers (n = 54)	1 (ref)	0.76 (0.52–1.11)	0.70 (0.46–1.08)	1.11 (0.70–1.78)	0.61 (0.22–1.75)	0.94 (0.47–1.86)	0.85
Liver cancer							
Ever smokers (n = 65)	1 (ref)	1.05 (0.60–1.84)	1.85 (1.05–3.25)	1.68 (0.84–3.34)	2.39 (0.91–6.32)	1.67 (1.00–2.79)	0.05
Never smokers (n = 48)	1 (ref)	1.06 (0.61–1.86)	1.86 (1.06–3.28)	1.69 (0.85–3.37)	2.45 (0.93–6.47)	1.67 (1.00–2.79)	0.05
Sex-specific cancer sites[c]							
Breast cancer							
Ever smokers (n = 2,947)	1 (ref)	1.11 (1.00–1.24)	1.09 (0.97–1.22)	1.08 (0.94–1.23)	0.88 (0.72–1.09)	0.92 (0.81–1.06)	0.24
Never smokers (n = 2,450)	1 (ref)	0.96 (0.86–1.07)	0.91 (0.81–1.03)	0.99 (0.86–1.15)	0.96 (0.76–1.21)	0.98 (0.83–1.15)	0.78
Endometrial cancer							
Ever smokers (n = 516)	1 (ref)	0.84 (0.65–1.09)	0.98 (0.75–1.27)	0.81 (0.58–1.11)	1.28 (0.86–1.89)	1.07 (0.83–1.39)	0.60
Never smokers (n = 549)	1 (ref)	0.98 (0.79–1.24)	0.97 (0.75–1.24)	0.86 (0.63–1.19)	0.96 (0.59–1.54)	0.96 (0.67–1.36)	0.81
Ovarian cancer							
Ever smokers (n = 323)	1 (ref)	1.05 (0.77–1.43)	0.91 (0.65–1.28)	1.08 (0.72–1.62)	0.90 (0.48–1.68)	0.92 (0.60–1.42)	0.72
Never smokers (n = 227)	1 (ref)	0.60 (0.42–0.85)	0.74 (0.51–1.07)	0.83 (0.52–1.33)	0.88 (0.41–1.88)	0.91 (0.51–1.64)	0.76
Advanced prostate cancer							
Ever smokers (n = 497)	1 (ref)	0.99 (0.78–1.26)	0.98 (0.75–1.29)	1.10 (0.79–1.52)	1.03 (0.58–1.84)	1.12 (0.79–1.58)	0.53
Never smokers (n = 459)	1 (ref)	1.20 (0.93–1.55)	1.31 (0.99–1.73)	0.92 (0.64–1.34)	1.00 (0.50–1.98)	0.82 (0.49–1.39)	0.47

NOTE: All models included for age, race (white or non-white), height (continuous), body mass index (quintiles), family history of cancer (yes or no), physical exam in past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking in pack-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or ≥40), physical activity (quintiles), regular aspirin use (yes or no), multivitamin use (yes or no), total energy intake (quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥30 g/d), red and processed meat intake (quintiles), prudent diet pattern (quintiles) and Western diet pattern (quintiles); prostate-specific antigen test in past 2 years (yes or no) for men only; and menopause status (premenopause or postmenopause), postmenopausal hormone use (never, past, or current), and mammogram in past 2 years (yes or no) for women only.

[a]Included only aggressive prostate cancer as total cancer.

[b]Pooled results of women and men.

[c]Sex-specific results of women (breast, endometrial, and ovarian cancers) and men (advanced prostate cancer).

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which strengthens the internal validity but may limit the generalizability of our findings.

In conclusion, we found no association of mushroom consumption with total and site-specific cancers in U.S. women and men. These findings suggest that the cancer protective effects of mushrooms described in *in vitro* and animal studies are likely to have minimal impact in terms of cancer prevention at a population level. Given that the most salient limitations of this study are the lack of specificity in mushroom assessment (i.e., variety of specific mushroom species, cultivation, and cooking practices), the lack of repeated measures of mushroom intake over time, and the lack of racial/ethnic diversity of the study population, future studies revisiting this hypothesis should ideally address these three issues.

Disclosure of Potential Conflicts of Interest

Q. Sun is a consultant/advisory board member for Emavant Solutions GmbH. J.E. Chavarro reports receiving other commercial research support from Horticulture Australia Limited (HAL). No potential conflicts of interest were disclosed by the other authors.

Disclaimer

Horticulture Australia Limited had no role in study planning, data collection, data analysis, interpretation of the findings, drafting of the article or decisions regarding where or when to publish study results.

Authors' Contributions

Conception and design: D.H. Lee, E.L. Giovannucci, J.E. Chavarro
Development of methodology: D.H. Lee, M. Yang, J.E. Chavarro
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.H. Lee, E.L. Giovannucci, Q. Sun, J.E. Chavarro
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.H. Lee, M. Yang, N. Keum, Q. Sun, J.E. Chavarro
Writing, review, and/or revision of the manuscript: D.H. Lee, M. Yang, N. Keum, E.L. Giovannucci, Q. Sun, J.E. Chavarro
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.H. Lee, J.E. Chavarro
Study supervision: J.E. Chavarro

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