Mushroom consumption and risk of total and site-specific cancer in two large US prospective cohorts

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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 risk. 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 (HRs) and 95% confidence intervals (CIs) 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 5 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 US women and men. More prospective cohort studies are needed to examine the associations for specific cancer types in diverse racial/ethnic groups.

Keywords

Mushroom; diet; nutrition; cancer; cohort study

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. Moreover, the existing evidence is largely from relatively small studies from Asian countries. More prospective studies are warranted in diverse population 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 US 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 US female nurses aged 30 to 55 years in 1976. The Health Professionals Follow-up Study (HPFS) is a parallel cohort study which included 51,529 US male health professionals aged 40 to 75 years in 1986. Participants were asked to complete a mailed questionnaire at enrollment and every two years thereafter to assess information on demographics, lifestyle factors and medical history. Dietary data were assessed every four 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 3500 for women; <800 or 4200 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. 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 de-attenuated correlation comparing mushroom intake recorded in multiple prospectively collected diet records to mushroom intake reported in the FFQ was 0.65 and the average de-attenuated 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 anatomical 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 5 categories as follows: (1) Never or less than once per month (almost never), (2) Less than once a week, (3) Once a week, (4) 2–4 times a week, (5) 5+ times a week. We also used mushroom consumption as a continuous variable (i.e., per 2 servings/week increase).

Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence interval (CIs) 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 two 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 two years (yes or no) for men

and menopausal status (pre-menopause or post-menopause), postmenopausal hormone use (never, past, or current), and mammogram in past two 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 variable in the models (P>0.05). Since 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, ovarian cancers for women and advanced prostate cancer for men). Lastly, we conducted stratified analysis by smoking status to examine whether the association between mushroom consumption and risk of cancer differ by smoking status.

We used the SAS software (version 9.4, SAS Institute) for all analyses. All statistical tests were 2-sided and P<0.05 was considered statistically significant. Multiple comparison was adjusted using Bonferroni-corrected $P<2.8\times10^{-3}$ (0.05 divided by 18 cancer outcomes).(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 to participants who almost never consumed mushrooms, those who consumed 5 or more servings of mushrooms/week had no significantly different risk of total cancer (HR=1.06, 95% CI=0.98–1.14). Increasing mushroom intake by 2 servings/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 2 servings/week increase=1.17, 95% CI=1.00–1.36, P for trend=0.05).

We then evaluated the relation of mushroom intake 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 for trend=0.05) and never smokers (P for 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 2 servings/week increase=0.98, 95% CI=0.93–1.04) (Supplemental Table 1). 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 2 servings/week increase=1.10, 95% CI=1.00–1.21, P for trend=0.04) and liver cancer (HR per 2 servings/week increase=2.13, 95% CI=1.12–4.05, P for trend=0.02). These associations were not statistically significant after adjusting for multiple comparison (Supplemental Table 2). Other cancer sites were not associated with mushroom consumption in men.

Discussion

In the two large US 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 7 studies, including 5 case-control and 2 cohort studies, reported that increasing 1 gram 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).(8) Due to 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 to those with low mushroom consumption (<25th percentile) (RR=0.30, 95% CI=0.15–0.62, P for trend<0.001).(16) Similarly, a Japanese study showed an inverse, but marginally significant, association of specific type of mushrooms (Hypsizigus 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, legumes and legume products) were associated with decreased risk of liver cancer. Compared to 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 for 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 to prospective cohort studies,(19,20) retrospective case-control studies(21–25) tended to show a significant or suggestive inverse association between mushroom 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 to 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, if 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 non-differential, 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 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 US 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1.

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

Characteristic	Frequency of mushroom consumption, per serving				
	Never or Almost never	<1/week	1/week	2–4/week	5+/week
Women (NHS)					
No of person	15318	22614	18376	9100	2919
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)
Post-menopause (%)	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 h/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)	1553 (505)	1536 (488)	1567 (483)	1602 (483)	1625 (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	9962	16106	11708	5763	1125
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 h/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)

Characteristic	Frequency of mushroom consumption, per serving				
	Never or Almost never	<1/week	1/week	2–4/week	5+/week
Calorie intake (kcal/day)	1906 (625)	1921 (594)	2036 (600)	2157 (635)	2298 (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

Abbreviation: HPFS, health professionals follow-up study; MET, metabolic equivalent task; NHS, nurses' health study.

Values are means (SD) or percentages and are standardized to the age distribution of the study population (except for age).

[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.

Table 2.

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

	Frequency of mushroom consumption, per serving					Per 2/week increase	P-trend
	Never or almost never	<1/week	1/week	2–4/week	5+/week		
Total cancer (n=22469)[a,b]							
Event	4981	7688	5938	3009	853		
Person years	516441	803462	631961	310373	84651		
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=2342)							
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=2036)							
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=1456)							
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=1001)							
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]							

	Frequency of mushroom consumption, per serving					Per 2/week increase	P-trend
	Never or almost never	<1/week	1/week	2–4/week	5+/week		
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

	Frequency of mushroom consumption, per serving					Per 2/week increase	P-trend
	Never or almost never	<1/week	1/week	2–4/week	5+/week		
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=5397)							
Event	1148	1818	1466	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=1065)							
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
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

Abbreviation: HPFS, health professionals follow-up study; NHS, nurses' health study.

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), 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 two years (yes or no) (men only); and menopause status (pre-menopause or post-menopause), postmenopausal hormone use (never, past, or current), and mammogram in past two years (yes or no) (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).

Table 3.

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

	Never or almost never	Frequency of mushroom consumption, per serving					Per 2/week increase	P-trend
		<1/week	1/week	2–4/week	5+/week			
Total cancer [a,b]								
Ever smokers(n=13365)	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=9104)	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=1376)	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=1732)	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

	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
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=2947)	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=2450)	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

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 two 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 two years (yes or no) (men only); and menopause status (pre-menopause or post-menopause), postmenopausal hormone use (never, past, or current), and mammogram in past two years (yes or no) (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).