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Mushroom Consumption and Risk of Gastric Cancer—A Pooled Analysis within the Stomach Cancer Pooling (StoP) Project and a Combined Meta-Analysis with other Observational studies

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Abstract

Edible mushrooms have high concentrations of vitamins and minerals. They are considered “functional foods” for their disease prevention properties. Mushroom consumption may reduce the risk of gastric cancer, the fifth most common cancer worldwide. We investigated the association between mushroom consumption and gastric cancer risk in a pooled-analysis within the Stomach Cancer Pooling (StoP) Project and in a meta-analysis that also included previously published studies. A total of 3,900 gastric cancer cases and 7,792 controls from 11 studies were included in the StoP analysis. Mushroom consumption was measured using food frequency questionnaires (FFQ). Higher mushroom consumption was associated with a lower risk of gastric cancer (relative risk [RR] for the highest vs. lowest consumption categories: 0.82, 95% confidence interval [CI]: 0.71-0.95). The corresponding RRs were 0.59 (95% CI: 0.26-1.33) in a meta-analysis of 4 previously published studies, and 0.77 for all studies combined (95% CI: 0.63-0.9, n=15 studies). In geographic subgroup analysis, the pooled risk in Western Pacific countries was (RR=0.59, 95% CI: 0.40-0.87, n=6). The stronger effect in Asian countries may reflect high level of antioxidants in mushroom species consumed in Asia.

Keywords

Epidemiology; Gastric cancer; meta-analysis; mushrooms; pooled-analysis

Introduction

Mushrooms are low in energy, fat, and high in fiber, essential vitamins (e.g., thiamin and vitamin C)([Mattila et al., 2000,Kalaras et al., 2012b]), and trace minerals([Beelman and Royse, 2006,Jo Feeney et al., 2014a]). They are considered a food that is part of a healthy eating pattern([Carol E O'Neil, 2013]) and are enjoyed for their unique taste, subtle flavor, and nutritional value([Dolai et al., 2008]). They are a good source of ergocalciferol (vitamin D_2) when exposed to UV light during the growing phase and post-harvest([Kalaras et al., 2012a,Cardwell et al., 2018]) and are also sources of other under-consumed micronutrients including calcium and potassium([Jo Feeney et al., 2014b]). Although mushrooms share some nutritional characteristics with plant-derived foods, they are biologically distinct as fungi. They are a source of specific bioactive compounds including the antioxidants ergothioneine (ERGO) and glutathione. Oxidative stress has been associated with the pathogenesis of chronic diseases, including cancers([Perše, 2013]). Mushrooms have anti-cancer properties including reducing cellular proliferation through several mechanisms including reducing oxidative stress([Patel and Goyal, 2012]).

One cancer type that mushroom consumption may prevent is stomach (gastric cancer). The incidence rate of stomach (gastric) cancer has steadily declined worldwide, yet it is still the fifth most commonly diagnosed cancer globally, with an estimated over 1 million new cases in 2020 (5.6%). Stomach cancer is the fourth leading global cause of cancer death (7.7%) ([Hamashima, 2020,Sung et al., 2021]). The highest incidence rates are in East Asian countries such as China, Korea, and Japan([Hamashima, 2020]). Infection with *Helicobacter pylori* (*H. pylori*) occurs in at least 95% of all gastric cancers([Wroblewski et al., 2010,Shiotani et al., 2013]) and in more than 50% of the world's population([Hooi et al., 2017]). One of the mechanisms of *H. pylori*-induced gastric cancer is chronic oxidative stress([Butcher et al., 2017]). There are few epidemiologic studies of mushroom consumption and stomach cancer. In Korea, a reduced risk of gastric cancer was found with mushroom consumption([Park et al., 1998,Kim et al., 2002]). However, the results of other studies were inconclusive([Ko et al., 2013,Lee et al., 2019]).

Given the limited research in this area, we conducted a pooled analysis within the Stomach Cancer Pooling (StoP) Project([Pelucchi et al., 2015]) (unpublished data) and a meta-analysis of previously published studies. We hypothesized that higher mushroom consumption is associated with a lower risk of stomach cancer.

Methods

Stomach Cancer Pooling (StoP) Project

Data source and study population—The pooled analysis is based on the third database release of the StoP Project, which is a consortium of case-control studies (including nested case-control within cohort studies). The third release included 34 studies that included

13,121 cases and 31,420 controls. The StoP project examines the role of lifestyle factors and genetic variability in the etiology of gastric cancer through pooled analyses of individual-level data. All data were collected and harmonized according to a prespecified format at the pooling center. The StoP Project received ethical approval from the University of Milan Review Board (reference 19/15 on 01/04/2015), and detailed information is described elsewhere([Pelucchi et al., 2015]). Restrictions apply to the availability of these data, which were provided by the authors for this analysis and are subject to third party limitations.

For the current analyses, individual-level data from 11 studies with information on mushroom intake was used, including 3,900 cases and 7,792 controls, from Brazil (two studies)([Hamada et al., 2002,Nishimoto et al., 2002]), China (two)([Mu et al., 2005,Setiawan et al., 2005]), Greece([Lagiou et al., 2004]), Italy([Buiatti et al., 1989]), Japan([Machida-Montani et al., 2004]) Mexico([López-Carrillo et al., 2003]), Russia([Zaridze et al., 2000]) (one study each), and Spain(two studies)([Santibañez et al., 2012,Castaño-Vinyals et al., 2015]).

Mushroom consumption and covariate assessment—Mushroom consumption was measured by study-specific food frequency questionnaires (FFQ). The majority of the included studies reported that the FFQ used was previously validated by comparison with multiple 24-hr recall dietary records([Ferro et al., 2020]). Each study-specific FFQ used slightly different categories of mushroom intake (e.g., never vs less than one per month as the lowest category). For pooling, mushroom consumption was categorized into 3 groups (lowest, middle, and highest) based on the distribution of intake within each individual study. For four studies the distribution of intake was bivariate and grouped into two categories.

The following covariates were included in the individual-level data analysis whenever available: sex (men/women), age, socioeconomic status (low, intermediate or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers), body mass index (BMI) categories (<24.9, 25.0–29.9, ≥ 30 kg/m2), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: >12–47 g of ethanol/day, high: >47 g of ethanol/day), vegetable and legume consumption (study-specific tertiles), fruit consumption (study-specific tertiles), total energy intake (tertiles), history of diabetes (yes/no). Dietary covariates were assessed using FFQ. The demographic and lifestyle covariates were evaluated by questionnaires.

Statistical analysis

Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA. Statistical tests were reported as significant at p values less than 0.05 and were two-sided. Descriptive analysis was conducted to present the characteristics of the studies by case and control status. To assess the association of mushroom consumption with stomach cancer, multivariable unconditional logistic regression models were performed to generate the odds ratios (OR) and the corresponding 95% confidence intervals (CIs) for each study. To estimate the effect of confounding variables, we calculated the overall crude ORs and compared that to the risk adjusted for covariates.

Meta-Analysis

R statistical software (R Team) using the packages “meta” and “metafor” was used for meta-analyses. Summary effects estimates were calculated as weighted averages of each individual study’s ORs using random-effects models. One study conducted in Japan([Machida-Montani et al., 2004]) had information about four mushroom species (Corrinellus shiitake, Flammulina velutipes, Hypsizigus marmoreus, and Pholita nameko). In this situation, we combined the effect estimates of the four mushroom species using a random-effects model to get overall estimates.

For each individual study, we calculated the odds ratios for the highest vs. lowest category of consumption. Random-effects meta-analysis models were conducted to obtain the summary estimate using the DerSimonian and Laird's method([DerSimonian and Kacker, 2007]). The presence of statistical heterogeneity across studies was assessed using the Cochran’s Q test and further quantified using the I^2 statistics expressed as a proportion (%) ([Higgins and Thompson, 2002]).

To explore potential source of heterogeneity, sub-group analyses were performed to assess the risk by World Health Organization (WHO) geographic regions (Africa, Americas, Eastern Mediterranean, Europe, Southeast Asia, and Western Pacific), World Bank Income group (low, lower-middle, upper middle, high), and study design (case-control, cohort).

Publication bias was evaluated by examining the symmetry of funnel plots and using Egger’s and Begg tests([Egger et al., 1997]). A pre-specified sensitivity analysis was performed. Duval and Tweedie’s trim and fill modification was applied to account for small-study effects and applied the leave-one-out method to adjust for potential outlying and influential studies([Kirkland et al., 2004]). Lastly, we assessed the association of specific mushroom species and gastric cancer in Japan.

Meta-analysis of previously published data

Data on four previously published ([Park et al., 1998],[Kim et al., 2002],[Ko et al., 2013],[Lee et al., 2019]) on mushroom intake and gastric cancer were extracted. The search strategy, criteria and data extraction protocols were previously described([Ba et al., 2021]). The RRs were calculated using the same methodology of comparing the highest vs lowest categories of consumption. Data from the StoP Japan study was previously published and therefore excluded from the met-analysis of previously published studies.

Finally, all StoP and published studies were combined to calculate summary risk estimates (RRs) and 95% confidence intervals (CIs).

Results

StoP project study characteristics

The main characteristics of the 3,900 gastric cancer cases and 7,792 controls included in the current analysis are shown in Table 1. Approximately more than half of the cases and controls were from European studies. Nearly two-thirds of gastric cancer cases (63.4%) were men and had lower socioeconomic status than controls (63.4 vs. 58.6%). They also had

higher alcohol consumption than controls (10.5 vs. 7.5%) and were more frequently current smokers (29.0 *vs.* 24.2%). In addition, they had lower mushroom intake than controls (53.7 vs. 56.1).

StoP Project pooled analysis results

When crude estimates for the highest vs. lowest were pooled for the StoP Project studies (n= 11), the risk of stomach cancer was 27% lower in the highest vs. lowest mushroom consumption group (RR=0.73, 95% CI: 0.65-0.81) (eFig 1). For the adjusted estimate, higher mushroom consumption was associated with a lower risk of cancer (RR= 0.82, 95%CI: 0.71-0.95, n=11) (Fig. 1). There was low heterogeneity between StoP Project studies (I^2: 18%, p=0.27).

Previous studies and combined StoP results

The adjusted RR from four previous studies are shown in Fig 1. The summary RR was 0.59 (95% CI: 0.26-1.33). The adjusted RR from these studies and the StoP Project studies combined was 0.77 (95% CI: 0.63-0.95, n= 15) (Fig 1). The overall between-study heterogeneity was modest (I^2: 55%, p=0.01).

Combining both StoP and the previous studies, a meta-analyses of risk estimates by WHO geographic regions showed that higher mushroom consumption was associated with a lower adjusted risk of stomach cancer in the Western Pacific region (RR=0.59; 95% CI: 0.40-0.87, n=6, Fig 2). The risk was (RR= 0.93; 95% CI: 0.74-1.16, n=5) in the European region and (RR=0.88; 95% CI: 0.53-1.46, n=4) in the American region.

Further subgroup analysis of StoP and published studies (Table 2) found a statistically significant lower adjusted risk of stomach cancer with high mushroom intake in case-control studies and in studies that did not adjust for total energy intake. There was no significant association in the two cohort studies (RR=1.27, 95% CI: 0.70-2.31) (eFig 2) and in studies that adjusted for total energy (RR=0.84, 95% CI: 0.69-1.03) (eFig 3). Analysis stratified by World Bank income group showed no differences, with a RR of 0.75 (95% CI: 0.55-1.02) for HIC and a RR of 0.87 (95% CI: 0.72-1.06) for LMIC studies (eFig 4).

Visual inspection of a funnel plot including all 15 studies (eFig 5), and the use of Egger's and Begg's tests, revealed no evidence of asymmetry (t = −0.50, df = 13, p-value = 0.96) and (z = 0.25, p-value = 0.80), respectively. This observation was further confirmed by a lack of additional studies in Duval and Tweedie's trim and fill modification. Sensitivity analyses using the leave-one-out method did not indicate any influential or outlier study (RR=0.77, 95%CI: 0.63-0.95) (eFig 6).

A meta-analysis of mushroom species consumed in Japan showed similar protective effects between mushroom species. The corrinellus shiitake mushrooms had the lowest relative risk (RR=0.45, 95% CI: 0.20-1.02) (eFig 7).

Discussion

In this pooled-analysis including 11 studies within the StoP Project and four additional published studies, the highest level of mushroom consumption was associated with a lower risk of gastric cancer. Geographical region analysis showed decreased RR primarily in Western Pacific countries such as Korea, China and Japan. No significant association was found between higher mushroom consumption and gastric cancer in studies conducted in European or American countries. There are thousands of edible mushroom species consumed worldwide. A variety of both dried and fresh mushrooms are commonly consumed in Asia. One possible explanation for the more pronounced protective effect against gastric cancer in Asian studies is the high consumption of shiitake, oyster, maitake, and king oyster mushrooms compared to the white button, crimini, and portabellas mushrooms which are more commonly consumed in European and American countries([Beelman et al., 2019]). Alternatively, mushrooms may be part of a more plant-based Asian diet that confers a protective effect against cancer.

Mushrooms contain numerous beneficial nutrients and some compounds such as the polysaccharide β-glucans([Meng et al., 2016]) which have antitumor properties([Zhang et al., 2007,Cao et al., 2013]). Cao and colleagues suggested that *Pleurotus ostreatus* mycelium (oyster mushroom) which contain the polysaccharides POMP2 may inhibit gastric cancer cell growth *in vitro and in vivo*([Cao et al., 2015]). Mushroom have high levels of ergothioneine, an amino acid with potent antioxidant properties([Beelman et al., 2019]). Ergothioneine is consumed exclusively through dietary sources([Ey et al., 2007,Paul and Snyder, 2010,Weigand-Heller et al., 2012,Feeney et al., 2014,Beelman et al., 2019]), with concentrations differing between mushrooms species. The highest concentrations are found in Asian mushrooms, particular shiitake mushrooms which had the most protective effect in species-specific analysis. Mushrooms are also a rich source of other antioxidants including glutathione, selenium, vitamin C, and vitamin D_2([Cardwell et al., 2018]). Mushroom extracts from some species reduce the ability of *H. pylori* to neutralize the acidic environment of the stomach([Kim et al., 1996]). There is little data on mushroom intake and *H. pylori* infection. A high carbohydrate diet in China was found to increase the risk of infection where a balanced diet that includes mushrooms did not affect the risk([Xia et al., 2016]).

The strengths of the current study include a large sample size and comprehensive analysis of mushroom intake and gastric cancer across a wide geographic area. For the StoP Project consortium, the data has undergone a harmonization process that facilitated the pooling of the studies. The observed associations for the pooled adjusted models were similar to the crude effect models, suggesting that unmeasured confounding likely had little effect on the results. In addition, we were able to show for the first time the effects of different mushroom species on gastric cancer.

The study also has several limitations. First, the interpretation of the findings needs to account for the lack of a lowered risk of gastric cancer in the two published cohort studies. One of the cohort studies was conducted in the US, and it is possible that the low levels of ergothioneine in mushroom species consumed in the US may not have a protective effect. In

addition, the statistical analysis of mushroom intake in all studies were based on quantiles, where the upper quantile of consumption in the US is likely less than the upper quantile consumption in Asian countries. Second, we were not able to conduct a dose-response meta-analysis because only 2 of 16 studies reported mushroom intake as grams/day and the others reported the units by servings. Serving sizes differ globally([Yamoah et al., 2019]), and we did not have a method of standardization to account for these differences. Confounding did not appear to affect the findings as evidenced by the similar results between the crude and adjusted estimates. Lack of adjustment for total energy in nutritional studies may overestimate the strength of associations([Willett et al., 1997]). In subgroup analysis the protective effect was not as strong for studies that adjusted for total energy vs. those that did not, although the heterogeneity was not significant.

In conclusion, the current collaborative analysis including 11 studies within the StoP Project and four additional studies show that higher mushroom consumption was associated with a lower risk of gastric cancer, primarily in Asian countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence interval
FFQ	food frequency questionnaire
H. pylori	Helicobacter pylori
OR	odds ratios
RR	relative risk
StoP	Stomach Cancer Pooling Project
WHO	World Health Organization

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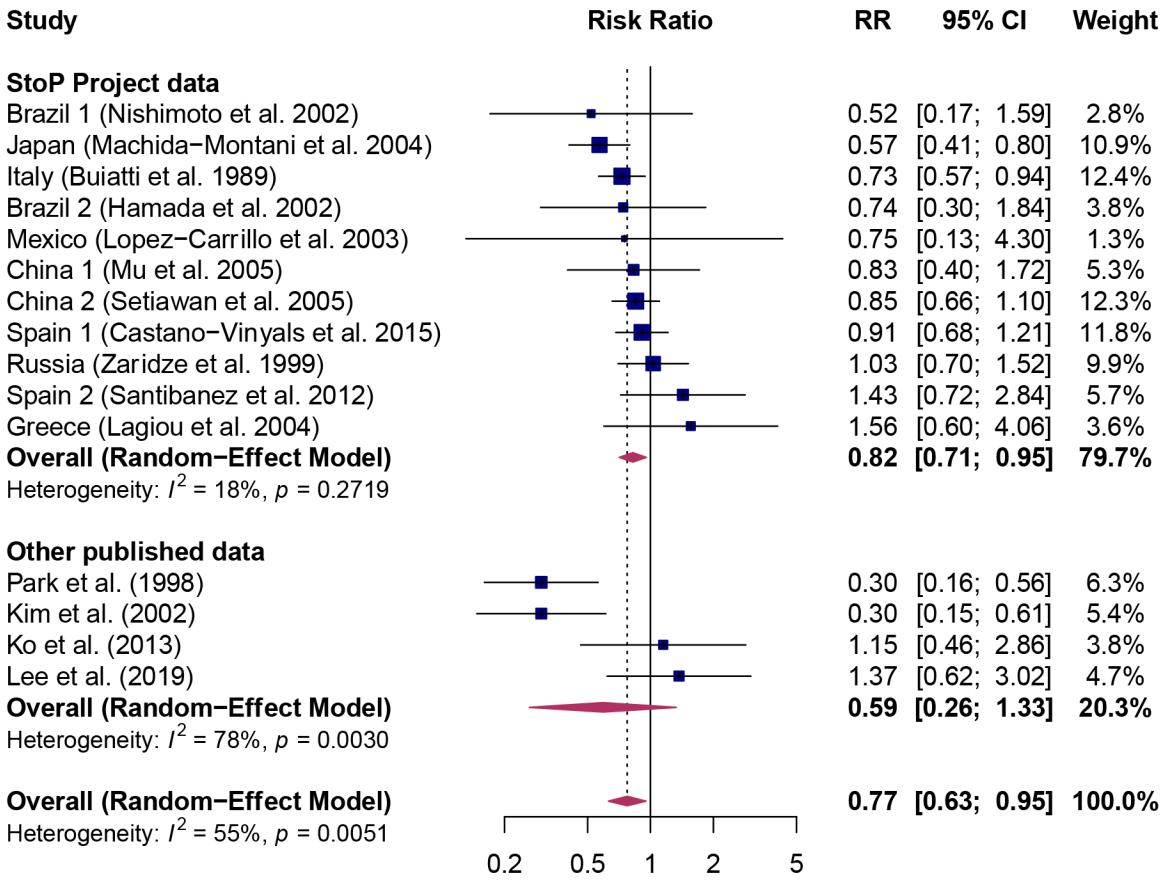

Fig 1. Association of mushroom consumption (highest vs. lowest categories) with risk of gastric cancer.

Blue squares and their corresponding lines are the point estimates and 95% confidence intervals for each study. Maroon diamond represented pooled effect estimate for each subgroup.

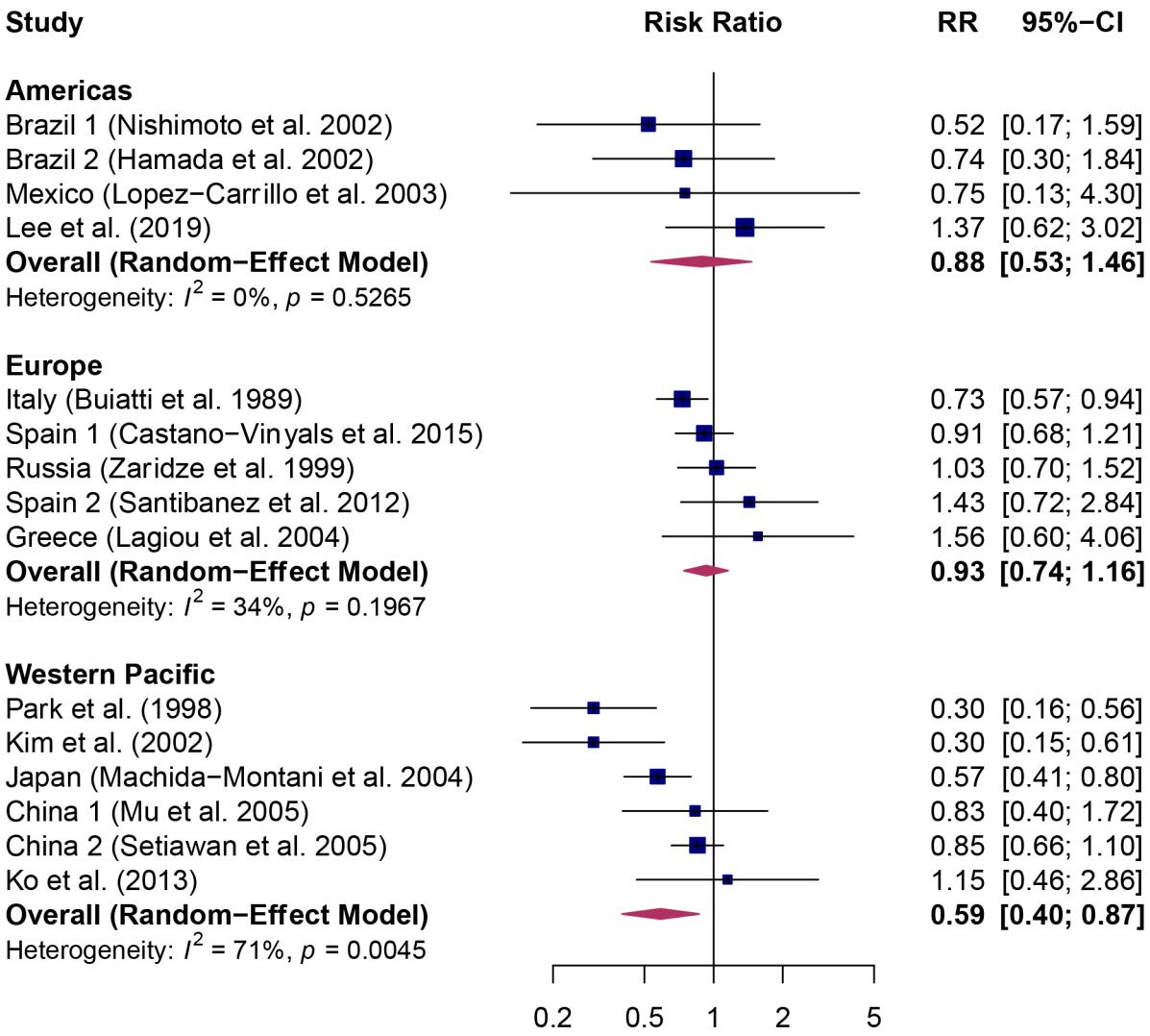

Fig 2. Association of mushroom consumption (highest vs. lowest categories) with risk of gastric cancer stratified by the WHO region.

Blue squares and their corresponding lines are the point estimates and 95% confidence intervals for each study. Maroon diamond represented pooled effect estimate for each subgroup.

Table 1

Distribution of 3,900 cases of gastric cancer and 7,792 controls according to study center, sex, age and other selected covariates.

	Cases		Controls	
	N	%	*N*	%
Total	3,900		7,792	
Study center				
Europe				
Italy (Buiatti et al. 1989)	1,016	26.1	1,159	14.9
Greece (Lagiou et al. 2004)	110	2.8	100	1.3
Spain 1 (Castano-Vinyals et al. 2015)	441	11.3	3,440	44.2
Spain 2 (Santibanez et al. 2012)	401	10.3	455	5.8
Russia (Zaridze et al. 1999)	450	11.5	611	7.8
Asia				
China 1 (Mu et al. 2005)	206	5.3	415	5.3
China 2 (Setiawan et al. 2005)	711	18.2	711	9.1
Japan (Machida-Montani et al. 2004)	153	3.9	303	4.0
Americas				
Brazil 1 (Nishimoto et al. 2002)	226	5.8	226	2.9
Brazil 2 (Hamada et al. 2002)	93	2.4	186	2.4
Mexico (Lopez-Carillo et al. 2003)	93	2.4	186	2.4
Age, mean (SD)	62.9 (10.9)		62.0 (11.5)	
Sex				
Men	2,474	63.4	4,564	58.6
Women	1,426	36.6	3,228	41.4
Socioeconomic status				
Low	2,388	61.2	3,946	50.6
Intermediate	1,192	30.6	2,634	33.8
High	291	7.5	1,174	15.1
Missing	29	0.7	38	0.5
Smoking status				
Never	1,724	44.2	3,629	46.6
Former	979	25.1	2,176	27.9
Current	1,131	29.0	1,888	24.2
Missing	66	1.7	99	1.3
BMI (kg/m^2) [1]				
<24.9	1,695	43.5	3,243	41.6
25.0-29.9	873	22.4	2,336	30.0
≥ 30.0	920	23.6	1,615	20.7
Missing	412	10.6	598	7.7
History of diabetes [2]				

	Cases		Controls	
	N	%	*N*	%
Total	3,900		7,792	
No	3,226	82.7	6,290	80.7
Yes	256	6.6	776	10.0
Missing	418	10.7	726	9.3
Alcohol intake [3]				
Never	915	23.4	1,780	22.8
Low (≤12 g/d)	530	13.6	2,028	26.0
Intermediate (>12–47 g/d)	1,178	30.2	1,979	25.4
High (> 47 g/d)	408	10.5	581	7.5
Missing	869	22.3	1,424	18.3
Mushroom intake				
No	1,609	41.3	2,836	36.4
Yes	2,093	53.7	4,374	56.1
Missing	198	5.1	582	7.5
Vegetables/legumes intake [4]				
Low	1,106	28.3	1,961	25.2
Intermediate	1,098	28.2	2,304	29.6
High	1,469	37.7	2,624	33.7
Missing	227	5.8	903	11.6
Fruit intake [5]				
Low	1,247	32.0	2,097	26.9
Intermediate	1,143	29.3	2,275	29.2
High	1,229	31.5	2,616	33.6
Missing	281	7.2	804	10.3
Total energy intake [6]				
1st Tertile	875	22.4	2,024	26.0
2nd Tertile	952	24.4	1,954	25.1
3rd Tertile	980	25.1	1,924	24.7
Missing	1,093	28.0	1,890	24.3

[1] No information for the studies Mexico, Brazil 1, and Brazil 2.

[2] No information for the studies China 1 and Mexico.

[3] No information for the study China 2

[4] No information for the study Mexico

[5] No information for the study Mexico

[6] No information for the studies China 1, Russia, Brazil 1, and Brazil 2

Table 2.

Results of subgroup analysis for the association between mushroom intake (highest vs. lowest categories) and gastric cancer risk.

Subgroup	No. of studies	Pooled RR (95% CI)	I^2 (%)	*P* for heterogeneity between subgroups
Study design				0.09
Cohort	2	1.27 (0.70, 2.31)	0	
Case-control	13	0.74 (0.60, 0.92)	58	
WHO region				0.13
Americas	4	0.88 (0.53, 1.46)	0	
Europe	5	0.93 (0.74, 1.16)	34	
Western Pacific	6	0.59 (0.40, 0.87)	71	
Total Energy				0.23
Adjusted	8	0.84 (0.69, 1.03)	41	
Not adjusted	7	0.62 (0.39, 0.99)	66	
World Bank income groups				0.41
HIC	9	0.75 (0.55, 1.02)	71	
LMIC	6	0.87 (0.72, 1.06)	0	