Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project

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Abstract

Tobacco smoking is a known cause of gastric cancer, but several aspects of the association remain imprecisely quantified. We examined the relation between cigarette smoking and gastric cancer risk using a uniquely large dataset of 23 epidemiological studies within the "Stomach cancer Pooling (StoP) Project", including 10,290 cases and 26,145 controls. We estimated summary odds-ratios (ORs) and the corresponding 95% confidence intervals (CIs) by pooling study-specific ORs using random-effects models. Compared to never smokers, the ORs were 1.20 (95% CI 1.09-1.32) for ever, 1.12 (95% CI 0.99-1.27) for former and 1.25 (95% CI 1.11-1.40) for current cigarette smokers. Among current smokers, the risk increased with number of cigarettes per day to reach an OR of 1.32 (95% CI 1.10-1.58) for smokers of more than 20 cigarettes per day. The risk increased with duration of smoking, to reach an OR of 1.33 (95% CI 1.14-1.54) for more than 40 years of smoking, and decreased with increasing time since stopping cigarette smoking (p for trend<0.01) and became similar to that of never smokers 10 years after stopping. Risks were somewhat higher for cardia than non-cardia gastric cancer. Risks were similar when considering only studies with information on *Helicobacter pylori* (HP) infection, and comparing all cases to HP+ controls only. This study provides the most precise estimate of the detrimental effect of cigarette smoking on gastric cancer risk based on individual data, including the relationship with dose and duration, and the decrease in risk following stopping smoking.

Keywords: Consortia, Epidemiology, Pooled analysis, Tobacco smoking, Stomach neoplasms

Introduction

Tobacco smoking has been causally linked to gastric cancer (IARC Working Group, 2012). Two meta-analyses of published literature considering, respectively, 32 cohort (Ladeiras-Lopes *et al.*, 2008) and 46 case-control studies (La Torre *et al.*, 2009) showed a significant increase in risk of gastric cancer among smokers, though quantification of dose-response relations remains imprecise.

Risk of gastric cancer was reported to increase with increasing dose and duration of cigarette smoking in some studies (Gonzalez *et al.*, 2003; Ladeiras-Lopes *et al.*, 2008; Tramacere *et al.*, 2011; Nomura *et al.*, 2012). Furthermore, some studies showed a stronger association between cigarette smoking and gastric cardia rather than non-cardia cancer (Gonzalez *et al.*, 2003; Freedman *et al.*, 2007; Nomura *et al.*, 2012), but others did not confirm this finding (Lindblad *et al.*, 2005; Steevens *et al.*, 2010).

Lower risks have been generally found in former compared to current smokers, and the risk seems to decrease with increasing years since stopping smoking, although such relationship was not significant in several studies (Gonzalez *et al.*, 2003; Koizumi *et al.*, 2004; Freedman *et al.*, 2007; Kim *et al.*, 2007; Zendehdel *et al.*, 2008; IARC Working Group, 2012).

To better define and quantify the association between cigarette smoking and gastric cancer, we conducted an individual participant data meta-analysis of studies participating to the "Stomach cancer Pooling (StoP) Project", a recently established consortium of epidemiological studies on risk factors for gastric cancer.

Methods

This analysis is based on data from 23 case-control studies included in the first release of the "StoP Project" dataset, including 10,290 cases (6804 men, 3486 women) and 26,145 controls (15,600 men, 10,545 women) from Greece (Lagiou *et al.*, 2004), Italy (4 studies) (Buiatti *et al.*, 1989; La Vecchia *et al.*, 1995; Lucenteforte *et al.*, 2008; De Feo *et al.*, 2012), Portugal (Lunet *et al.*, 2007), Russia (Zaridze *et al.*, 2000), Spain (2 studies) (Santibanez *et al.*, 2012; Castano-Vinyals *et al.*, 2015), Sweden (3 studies, 2 of which were nested in cohort studies) (Ye *et al.*, 1999; Harris *et al.*, 2013), China (4 studies) (Setiawan *et al.*, 2000; Mu *et al.*, 2005; Setiawan *et al.*, 2005; Deandrea *et al.*, 2010), Iran (3 studies) (Derakhshan *et al.*, 2008; Pourfarzi *et al.*, 2009; Pakseresht *et al.*, 2011), Japan (Matsuo *et al.*, 2013), Canada (Mao *et al.*, 2002), and USA (2 studies) (Zhang *et al.*, 1999). Detailed information on the aims and methods of the "StoP Project" has been given elsewhere (Pelucchi *et al.*, 2015).

The principal investigators of participating studies were asked to provide information about cigarette smoking status (never, former, and current smoker), number of cigarettes smoked per day, duration of smoking, and time since stopping smoking, when applicable. Data were harmonized according to a pre-specified format and completeness and consistency between variables were carefully checked. For the present analysis, ever cigarette smokers were defined as participants who had smoked at least 100 cigarettes in their lifetime or more than one cigarette per day for at least 1 year, independently of the type of cigarette smoked (e.g., cigarettes with or without filter, with blond or black tobacco, hand-rolled cigarettes, etc.). Smoked forms of tobacco other than cigarettes, i.e. cigar and pipes, were considered in a separate category. Two studies (Setiawan *et al.*, 2000; Derakhshan *et al.*, 2008) providing information on lifetime cigarette status (ever, never) only were not considered in the dose-risk analyses on intensity and duration. We also collected information on a list of additional variables to be introduced as confounders and to define subgroups.

For two cohort studies included in the StoP Project consortium, the Swedish Mammography Cohort and the Cohort of Swedish Men (Harris *et al.*, 2013), a nested case-control design was used by selecting 4 controls for each case, matched on age.

To estimate the association between cigarette smoking and gastric cancer, we used a two-stage modeling approach (Smith-Warner *et al.*, 2006). In the first stage, we assessed the association between cigarette smoking and gastric cancer for each study by estimating the odds ratios (ORs) and the corresponding 95% CIs using multivariable unconditional logistic regression models (for categorical variables). These models included, when available and appropriate, terms for age (<40, 40-44, 45-49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75 years), sex, education/social class (study-specific low, intermediate, high), race/ethnicity (White, Hispanic/Latino, Black/African American, other), alcohol drinking (never, low ≤12 gr/day, intermediate >12-≤47 gr/day, high >47 gr/day), fruit and vegetables consumption (study-specific tertiles) and study center (for multicentric studies). The list of study-specific confounders is reported in Supplementary Table 1.

In the second stage, summary (pooled) effects estimates were computed using a random-effect model, by computing a weighted average of the study-specific log(ORs) obtained in the first stage, using as weights the inverse of the sum of the study-specific log(ORs) variances and the between-study variance components (DerSimonian and Laird, 1986).

For categorical variables, heterogeneity between studies was evaluated using the Q test statistics and quantified using I^2, i.e. the proportion of total variation contributed by between-study variance (Higgins *et al.*, 2003).

To investigate whether the effect of smoking was heterogeneous across strata of selected covariates, we conducted analyses stratified by age (≤55, >55-≤65, >65), sex,

geographic area (Europe, Asia, America), cancer site (cardia, non cardia), cancer histotype (intestinal, diffuse, undifferentiated) and type of controls (hospital controls, population controls; controls from 2 nested case-control studies were considered together with the latter).

We also evaluated the influence of *H.pylori* infection on the relation between cigarette smoking and gastric cancer. We considered only studies with the information on *H.pylori* infection and compared the pooled ORs obtained using all controls with that obtained using only *H.pylori* positive controls (assuming all gastric cancer cases are positive for *H.pylori* infection.

We tested for the significance of linear trends across levels of smoking intensity and duration variables by estimating study-specific trends and using the Wald test *P value* deriving from the summary random-effects estimate (Smith-Warner *et al.*, 2006).

For continuous variables, we studied the functional form of the relation using one-order and two-order fractional polynomial models. The method was based on a two-stage procedure. In a first step, we fitted first-order and second-order fractional polynomial models to each study adjusting for the aforementioned confounders. This family of models includes the linear one. In the second step, the pooled dose-risk relation was estimated through a bivariate random effects model (Rota *et al.*, 2010). The best fitting model, i.e. the one minimizing the model deviance, was selected when the best fitting model was non linear (Royston *et al.*, 1999).

Results

Table 1 shows the distribution of cases and controls by study, sex, age and major selected potential confounding factors, for a descriptive purpose only. Cases were older than controls

(mean age ± SD: 63 ± 11 vs. 60 ± 13, respectively) and had a lower social class. Overall, 8.6% of cases reported a history of stomach cancer in first degree relatives and 11.2% reported consumption of 4 or more drinks/day of alcoholic beverages (i.e., >47 grams/day of ethanol).

Figure 1 gives a forest plot of the study-specific and the pooled ORs for gastric cancer risk on the basis of all 23 studies participating to the consortium. The pooled estimate was 1.20 (95% CI 1.09-1.32) for ever smokers compared to never smokers.

The pooled ORs of gastric cancer according to cigarette smoking habits are given in Table 2. Among 21 studies reporting information on former smoking status, the pooled ORs were 1.19 (95% CI 1.09-1.31) for ever cigarette smokers, 1.12 (95% CI 0.99-1.27) for former cigarette smokers and 1.25 (95% CI 1.11-1.40) for current smokers, compared with never smokers. Among current smokers, the risk increased with number of cigarettes smoked per day. Compared to never smokers, ORs were 1.08 (95% CI 0.91-1.28) for 1 to 10 cigarettes per day, 1.30 (95% CI 1.16-1.45) for 11 to 20 cigarettes per day and 1.32 (95% CI 1.10-1.58) for more than 20 cigarettes per day, with a significant trend in risk ($p<0.01$). The risk also increased with increasing duration of smoking (p-value for trend<0.01) with ORs of 1.04 (95% CI 0.94-1.16) for up to 30 years of smoking, 1.32 (95% CI 1.17-1.49) for 31 to 40 years of smoking and 1.33 (95% CI 1.14-1.54) for more than 40 years of smoking, as compared to never smokers. A significant decreasing trend in risk was found with increasing time since stopping cigarette smoking ($p<0.01$), taking current smokers as reference group.

Study-specific and pooled ORs of gastric cancer for former and current smokers according to cigarette smoking intensity are shown in Figure 2. Heterogeneity between studies was low to moderate (I^2 between 19% and 56%) across categories of consumption.

Figure 3 gives the modeled relation between smoking intensity (Panel A) and duration (Panel B) considered as continuous variables and gastric cancer risk. For both variables, the best fitting model was the one with powers p1=-2 and p2=2, i.e. $\log(OR)= \beta_1 X^{-2} + \beta_2 X^2$. The estimated regression coefficients were β_1= -0.00002 and β_2= 0.000023 for smoking intensity, β_1= -1.46E-06 and β_2= 0.000136 for duration. Overall, duration appeared to have a somewhat stronger effect on risk than intensity. These graphs suggest that the intensity- and duration-risk relationships have a strong non-linear component ($p<0.001$).

Stratified analyses according to smoking intensity are given in Figure 4 and Supplementary Table 2. The ORs for high intensity of cigarette smoking (i.e., >20 cigarettes per day) were similar in men (OR=1.44, 95% CI 1.00-2.08) and women (OR=1.42, 95% CI 1.18-1.72), and higher in subjects aged 56-65 years (OR=1.64, 95% CI 1.33-2.03) and in studies conducted in Asia (OR=1.71, 95% CI 1.08-2.71) than in the other groups. However, none of these differences was statistically significant. Risks of gastric cardia cancer were somewhat higher than those of non-cardia gastric cancer in former (ORs=1.30 and 1.05, respectively), light (ORs=1.71 and 0.96, respectively) and moderate cigarette smokers (ORs=1.55 and 1.21, respectively). For subjects reporting high intensity of cigarette smoking, the ORs were 1.58 for cardia (95% CI 1.11-2.24) and 1.29 for non-cardia (95% CI 1.03-1.61) gastric cancer, and when looking at histotype, 1.28 (95% CI 0.90-1.81) for diffuse-type and 1.57 (95% CI 1.12-2.20) for intestinal-type gastric cancer. Effects of cigarette smoking on gastric cancer risk did not materially change when considering only studies with information on *H.pylori* infection (>20 cigarettes per day, OR=1.40, 95% CI 0.91-2.15) even when the analysis was restricted to *H.pylori* positive controls (>20 cigarettes per day, OR=1.48, 95% CI 0.93-2.36). Risks for smoking appeared to be somewhat higher in studies with hospital controls (>20 cigarettes per day, OR=1.58, 95% CI 1.33-1.87) than in those with population controls (>20 cigarettes per day, OR=1.18, 95% CI 0.87-1.60).

Stratified analyses on smoking duration according to sex, age, geographic area, cancer site, cancer histotype, source of controls and *H.pylori* infection are given in Supplementary Table 3. When considering long-term smokers (i.e., >40 years of smoking), risks appeared to be higher in gastric cardia (OR=1.78, 95% CI 1.44-2.19) than in non-cardia (OR=1.19, 95% CI 0.97-1.46) cancer cases, and in studies with hospital controls (OR=1.64, 95% CI 1.29-2.10) than in those with population controls (OR=1.17, 95% CI 0.98-1.38).

Discussion

This global dataset confirms the association between cigarette smoking and gastric cancer risk. This is the largest individual participant analysis on stomach neoplasms, including comprehensive and uniform information on relevant covariates, and thus provides the most precise and valid estimates of several quantitative aspects of the association. A 25% excess risk of gastric cancer was found among current smokers. The risk significantly increased with cigarette smoking intensity and duration, to reach 32% for smokers of more than 20 cigarettes per day and 33% for smoking duration of more than 40 years, as compared to never smokers. The increase in risk was steeper for duration than for dose. The risk declined with time since stopping smoking and approached the level of never cigarette smokers about 10 years after quitting.

These results are generally consistent with previous meta-analyses. Our OR estimates for current cigarette smokers were, if anything, slightly lower than those based on published studies, which found risks ranging between 1.5 and 1.7 (Tredaniel *et al.*, 1997; Ladeiras-Lopes *et al.*, 2008; La Torre *et al.*, 2009; Bonequi *et al.*, 2013), resulting in an estimated worldwide population attributable fraction of 19.5% in men and 3.0% in women (Peleteiro *et al.*, 2015). Publication bias may have led to an over estimation of the risk in the published literature. In fact, only about one-third of the studies included in this pooled-analysis were

present in previous meta-analyses of case-control (La Torre *et al.*, 2009) or cohort studies (Ladeiras-Lopes *et al.*, 2008).

Concerning the dose-risk relation for intensity and duration, previous results are limited. A meta-analysis of cohort studies (Ladeiras-Lopes *et al.*, 2008) showed an increasing trend in risk with smoking intensity, with a relative risk (RR) varying from 1.3 for the lowest dose, to 1.7 for 30 cigarettes per day. A significant trend in gastric cancer risk with increasing duration was reported in the European Investigation into Cancer and Nutrition (EPIC) (Gonzalez *et al.*, 2003) and in the Multiethnic Cohort (MEC) study (Nomura *et al.*, 2012). Although the association of gastric cancer with smoking has been long recognized, this study confirms that the risk is modest even at high doses, in spite of the increasing dose-risk gradient. Although the association with cigarette smoking is weaker for gastric cancer than for lung cancer, our pooled analysis finds a stronger relation with duration than with dose, as it has been shown for lung cancer.

An interesting finding of our study is the lower gastric cancer risk for former smokers as compared to current smokers, in particular $\geq$10 years after stopping. This has been suggested by previous studies (Gonzalez *et al.*, 2003; Ladeiras-Lopes *et al.*, 2008; Nomura *et al.*, 2012) and adds stomach cancer to the list of diseases whose risk is favorably affected by stopping smoking.

This pooled analysis reported similar findings in men and women. With reference to the site of cancer, two large cohort studies reported a higher risk of gastric cardia than non-cardia cancer in current smokers (Gonzalez *et al.*, 2003; Nomura *et al.*, 2012). A recent meta-analysis including 10 studies on gastric cardia adenocarcinoma reported an over two-fold risk for smokers of more than 40 years compared to never smokers (Tramacere *et al.*, 2011). A differential role of smoking (besides *H.pylori* (Kamangar *et al.*, 2006)) in the aetiology of

different gastric cancer subsites has also been hypothesized to contribute to the diverging trends in risk of gastric cardia and non-cardia cancers over the last decades (Gonzalez *et al.*, 2003). In this investigation, though the ORs for high intensity cigarette smokers were not statistically heterogeneous between subsites (i.e., 1.40 for gastric cardia and 1.29 for gastric non-cardia cancer), the risk tended to be higher for gastric cardia and patterns tended to differ. In fact, gastric cardia cancer risk was increased and higher than that for non-cardia subsite in light to moderate smokers, in long-term smokers, and among former smokers. Thus, the dose-risk and time-risk relations might be different between gastric cardia and non-cardia cancer, suggesting underlying differences in biological mechanisms involved.

Many mechanisms may explain the effect of tobacco smoking on gastric cancer occurrence. Several carcinogens contained in tobacco products, including N-nitroso compounds, have been involved in the etiology of gastric cancer (Mirvish, 1995). In vitro, a carcinogenic effect of tobacco smoke on the gastric mucosa has been reported (Tayler and Piper, 1977). In a population-based gastroscopic screening study, smoking has also been significantly associated with the development of precursor lesion of gastric cancer, i.e. dysplasia, chronic atrophic gastritis and intestinal metaplasia, (Kneller *et al.*, 1992). In gastric cancer cases, levels of stable DNA adducts were significantly higher in the DNA of smokers than in that of non smokers (Dyke *et al.*, 1992). Some studies investigated gene interaction with tobacco smoking in gastric cancerogenesis. Polymorphisms of *GSTT1*, *SULT1A1*, *CYP1a1* and *NAT2* genes appear to be implicated in modulating individual's susceptibility between smoking and gastric cancer (Agudo *et al.*, 2006; Lee *et al.*, 2006; Boccia *et al.*, 2007). Furthermore the hypermethylation of *CDH1* gene was observed preferentially in gastric tumors from smokers rather than non-smokers (Poplawski *et al.*, 2008).

Among the strengths of the study, the "StoP Project" included original and individual data on smoking on over 10,000 cases and 26,000 controls, which provided a unique opportunity

to investigate and accurately quantify the dose- and time factors- risk relationships and, among former smokers, the pattern of risk with time since stopping. The individual level approach has several advantages as compared to study-level meta-analyses, specifically the availability of detailed and uniform information on important covariates (Ioannidis *et al.*, 2013). For instance, we were able to investigate the confounding effect of *H.pylori* infection by restricting the analysis to controls positive for *H.pylori* infection (all cases were supposed to be *H.pylori* infected). This sensitivity analysis confirmed the results of the main analysis, thus providing further evidence of a role of cigarette smoking independent from that of *H.pylori*. Confounding from other specific factors, such as consumption of salted and smoked foods, cannot entirely be ruled out. Also, we found a substantial heterogeneity between studies that was not explained by age, sex and geographic area. Among potential explanations for the reported heterogeneity is that the type of cigarettes commonly smoked (e.g., with or without filter, with blond or black tobacco, hand-rolled, etc.) varies in different countries, together with their variable tar and nicotine concentrations. We were not able to address the role of such factors, however, since only a minority of studies had available information on type of cigarette smoked. The association was, if anything, stronger in studies using hospital controls. This is reassuring since it has been suggested that smokers may be over represented among hospital controls given the higher hospitalization rates and longer hospital stays in smokers compared to non smokers.

In conclusion, this investigation confirms a detrimental, although modest, effect of cigarette smoking on gastric cancer risk, provides the most valid and precise estimates of dose-risk and duration-risk relations, and clearly shows a decrease in risk after stopping smoking, which is important for primary prevention.

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FIGURES LEGEND

Figure 1. Study-specific and pooled ORs and corresponding 95% confidence intervals of gastric cancer risk for ever smokers compared to never smokers in the Stomach cancer Pooling (StoP) Project consortium.

Figure 2. Study-specific and pooled ORs and corresponding 95% confidence intervals of gastric cancer risk for former smokers (a), smokers of up to 10 cigarettes (b), smokers of more than 10 to 20 cigarettes (c) and smokers of more than 20 cigarettes per day (d), compared to never smokers in the Stomach cancer Pooling (StoP) Project consortium.

Figure 3. Relation between intensity (a), duration of cigarette smoking (b) and risk of gastric cancer according to the best fitting fractional polynomial model, i.e. the one with powers p1=-2 and p2=2, in the Stomach cancer Pooling (StoP) Project consortium.

Figure 4. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to intensity of cigarette smoking in strata of sex, age, geographic area, cancer site, cancer histotype, *Helicobacter Pylori* infection and controls recruitment in the Stomach cancer Pooling (StoP) Project consortium.

Table 1. Distribution of 10,290 cases of gastric cancer and 26,145 controls according to study center, sex, age, and other selected covariates in the Stomach cancer Pooling (StoP) Project consortium.

	Cases		Controls	
	N	**%**	**N**	**%**
Total	10290		26145	
Study center (Reference)				
Europe	*5079*	*49.4*	*12664*	*48.4*
Greece (Lagiou *et al.*, 2004)	110	1.1	100	0.4
Italy 1 (La Vecchia *et al.*, 1995)	769	7.5	2081	8.0
Italy 2 (Lucenteforte *et al.*, 2008)	230	2.2	547	2.1
Italy 3 (De Feo *et al.*, 2012)	160	1.6	444	1.7
Italy 4 (Buiatti *et al.*, 1989)	1016	9.9	1159	4.4
Portugal (Lunet *et al.*, 2007)	692	6.7	1667	6.4
Russia (Zaridze *et al.*, 2000)	450	4.4	611	2.3
Spain 1 (Castano-Vinyals *et al.*, 2015)	441	4.3	3440	13.2
Spain 2 (Santibanez *et al.*, 2012)	401	3.9	455	1.7
Sweden 1 (Harris *et al.*, 2013)	88	0.9	352	1.3
Sweden 2 (Harris *et al.*, 2013)	161	1.6	644	2.5
Sweden 3 (Ye *et al.*, 1999)	561	5.5	1164	4.5
Asia	*3197*	*31.1*	*6234*	*23.8*
China 1 (Deandrea *et al.*, 2010)	266	2.6	533	2.0
China 2 (Mu *et al.*, 2005)	206	2.0	415	1.6
China 3 (Setiawan *et al.*, 2005)	711	6.9	711	2.7
China 4 (Setiawan *et al.*, 2000)	133	1.3	431	1.6
Iran 1 (Pourfarzi *et al.*, 2009)	217	2.1	394	1.5
Iran 2 (Pakseresht *et al.*, 2011)	286	2.8	304	1.2
Iran 3 (Derakhshan *et al.*, 2008)	118	1.1	119	0.5
Japan (Matsuo *et al.*, 2013)	1260	12.2	3327	12.7
North America	*2014*	*19.6*	*7247*	*27.7*
Canada (Mao *et al.*, 2002)	1182	11.5	5033	19.3
USA 1 (Zhang *et al.*, 1999)	132	1.3	132	0.5
USA 2 (unpublished data, J Muscat)	700	6.8	2082	8.0
Sex				
Male	6804	66.1	15600	59.7
Female	3486	33.9	10545	40.3
Age				
<40	355	3.4	1917	7.3
40-45	362	3.5	1542	5.9
45-50	608	5.9	2009	7.7
50-54	995	9.7	2700	10.3

55-59	1340	13.0	3128	12.0
60-64	1616	15.7	4079	15.6
65-69	1864	18.1	4240	16.2
70-75	1864	18.1	3857	14.8
≥75	1286	12.5	2673	10.2
Social class[1]				
Low	5416	52.6	10625	40.6
Intermediate	2697	26.2	7857	30.1
High	1242	12.1	5422	20.7
Missing	*935*	*9.1*	*2241*	*8.6*
History of stomach cancer in first degree relatives[2]				
No	5139	49.9	13092	50.1
Yes	885	8.6	1287	4.9
Missing	*4266*	*41.5*	*11766*	*45.0*
Vegetables and fruit intake[3]				
Low	3028	29.4	6812	26.1
Intermediate	3107	30.2	7649	29.3
High	2995	29.1	8224	31.5
Missing	*1160*	*11.3*	*3460*	*13.2*
Alcohol drinking (gr/day)[4]				
Never	2194	21.3	6231	23.8
Low (≤12)	2089	20.3	7296	27.9
Intermediate (>12 and ≤47)	2418	23.5	5429	20.8
High (>47)	1155	11.2	2313	8.8
Missing	*2434*	*23.7*	*4876*	*18.6*

[1]No information available for study Iran 3 (Derakhshan et al., 2008).

[2]No information available for studies China 1 (Deandrea et al., 2010), Canada (Mao et al., 2002), China 3 (Setiawan et al., 2005), Iran 3 (Derakhshan et al., 2008), USA 2 (unpublished data, J Muscat), Sweden 1 (Harris et al., 2013) and Sweden 2 (Harris et al., 2013).

[3]No information available for studies USA 1 (Zhang et al., 1999), China 4 (Setiawan et al., 2000), Iran 3 (Derakhshan et al., 2008).

[4]Alcohol drinking was not available in category of consumption for the study Iran 2 (Pakseresht et al., 2011), China 3 (Setiawan et al., 2005), Sweden 3 (Ye et al., 1999), China 4 (Setiawan et al., 2000), Iran 3 (Derakhshan et al., 2008).

Table 2. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to cigarette and tobacco smoking habits in the Stomach cancer Pooling (StoP) Project consortium.

	Cases		Controls		OR (CI 95%)[1]
	N	%	N	%	
Total	10290		26145		
Cigarette smoking status					
Never smoker	4261	41.4	11742	44.9	1
Ever cigarette smoker	5814	56.5	13910	53.2	1.20 (1.09-1.32)
Other than cigarette smoker	122	1.2	343	1.3	1.07 (0.76-1.51)
missing	*93*	*0.9*	*150*	*0.6*	
Total[2]	10039		25595		
Cigarette smoking status					
Never smoker	4122	41.1	11369	44.4	1
Ever cigarette smoker	5510	54.9	13539	52.9	1.19 (1.09-1.31)
Former cigarette smoker	2727	27.2	7361	28.8	1.12 (0.99-1.27)
Current cigarette smoker	2783	27.7	6178	24.1	1.25 (1.11-1.40)
Other than cigarette smoker	122	1.2	343	1.3	1.06 (0.76-1.48)
missing	*287*	*2.9*	*353*	*1.4*	
Intensity (cigarettes per day)[3]					
0 to ≤10	673	6.7	1738	6.8	1.08 (0.91-1.28)
>10 to ≤20	1310	13.0	2742	10.7	1.30 (1.16-1.45)
> 20 (median value: 30)	767	7.6	1582	6.2	1.32 (1.10-1.58)
missing	*320*	*3.2*	*469*	*1.8*	
P value for trend					0.0001
Cigarette smoking duration (years)					
0 to ≤30	2210	22.0	6947	27.1	1.04 (0.94-1.16)
>30 to ≤40	1420	14.1	3029	11.8	1.32 (1.17-1.49)
> 40 (median value: 47)	1660	16.5	2999	11.7	1.33 (1.14-1.54)
missing	*507*	*5.1*	*917*	*3.6*	
P value for trend					<0.0001
Total[4]	7657		18222		
Time since stopping cigarette smoking (years)					
Never smoker	3204	41.8	8185	44.9	1
0 to <10	656	8.6	1504	8.3	1.10 (0.92-1.31)
10 to <20	515	6.7	1392	7.6	1.04 (0.90-1.19)
≥ 20 (median value: 27)	615	8.0	1728	9.5	1.00 (0.84-1.19)
Other than cigarette smoker	122	1.6	343	1.9	
Missing	*248*	*3.2*	*453*	*2.5*	
P value for trend					0.26
Time since stopping cigarette smoking (years)					
Current cigarette smoker	2297	30.0	4616	25.3	1
0 to <10	656	8.6	1504	8.3	0.87 (0.72-1.05)

10 to <20	515	6.7	1392	7.6	0.80 (0.70-0.92)
≥ 20 (median value: 27)	615	8.0	1728	9.5	0.79 (0.63-0.99)
Other than cigarette smoker	122	1.6	343	1.9	
Missing	248	3.2	453	2.5	
P value for trend					0.007

[1]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available, for sex, age, race/ethnicity, social class, alcohol drinking, fruit and vegetable consumption and study center for multicentric studies. [2]Information on former/current smoking status was not available for studies China 4 (Setiawan et al., 2000) and Iran 3 (Derakhshan et al., 2008).

[3]Current smokers only.

[4]Time since stopping cigarette smoking was not available for studies Greece (Lagiou *et al.*, 2004), Canada (Mao *et al.*, 2002), China 1 (Deandrea *et al.*, 2010), Iran 1 (Pourfarzi *et al.*, 2009), Iran 2 (Pakseresht *et al.*, 2011), USA 1 (Zhang *et al.*, 1999), Sweden 1 (Harris *et al.*, 2013), and Sweden 2 (Harris *et al.*, 2013).

Figure 1

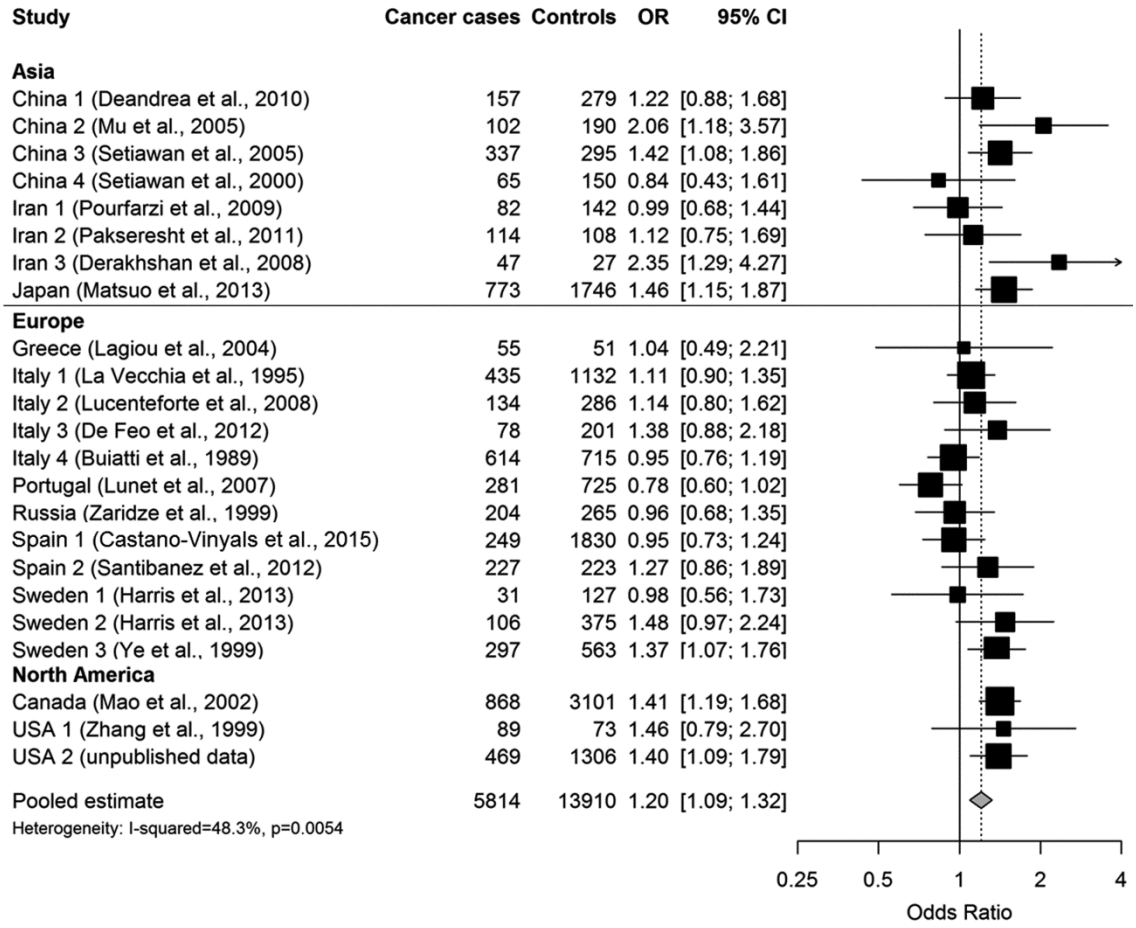

Study
Cancer cases
Controls
OR
95% CI
Asia
China 1 (Deandrea et al., 2010) 157 279 1.22 [0.88; 1.68]
China 2 (Mu et al., 2005) 102 190 2.06 [1.18; 3.57]
China 3 (Setiawan et al., 2005) 337 295 1.42 [1.08; 1.86]
China 4 (Setiawan et al., 2000) 65 150 0.84 [0.43; 1.61]
Iran 1 (Pourfarzi et al., 2009) 82 142 0.99 [0.68; 1.44]
Iran 2 (Pakseresht et al., 2011) 114 108 1.12 [0.75; 1.69]
Iran 3 (Derakhshan et al., 2008) 47 27 2.35 [1.29; 4.27]
Japan (Matsuo et al., 2013) 773 1746 1.46 [1.15; 1.87]
Europe
Greece (Lagiou et al., 2004) 55 51 1.04 [0.49; 2.21]
Italy 1 (La Vecchia et al., 1995) 435 1132 1.11 [0.90; 1.35]
Italy 2 (Lucenteforte et al., 2008) 134 286 1.14 [0.80; 1.62]
Italy 3 (De Feo et al., 2012) 78 201 1.38 [0.88; 2.18]
Italy 4 (Buiatti et al., 1989) 614 715 0.95 [0.76; 1.19]
Portugal (Lunet et al., 2007) 281 725 0.78 [0.60; 1.02]
Russia (Zaridze et al., 1999) 204 265 0.96 [0.68; 1.35]
Spain 1 (Castano-Vinyals et al., 2015) 249 1830 0.95 [0.73; 1.24]
Spain 2 (Santibanez et al., 2012) 227 223 1.27 [0.86; 1.89]
Sweden 1 (Harris et al., 2013) 31 127 0.98 [0.56; 1.73]
Sweden 2 (Harris et al., 2013) 106 375 1.48 [0.97; 2.24]
Sweden 3 (Ye et al., 1999) 297 563 1.37 [1.07; 1.76]
North America
Canada (Mao et al., 2002) 868 3101 1.41 [1.19; 1.68]
USA 1 (Zhang et al., 1999) 89 73 1.46 [0.79; 2.70]
USA 2 (unpublished data) 469 1306 1.40 [1.09; 1.79]
Pooled estimate 5814 13910 1.20 [1.09; 1.32]
Heterogeneity: I-squared=48.3%, p=0.0054
0.25
0.5
1
2
4
Odds Ratio

Figure 2

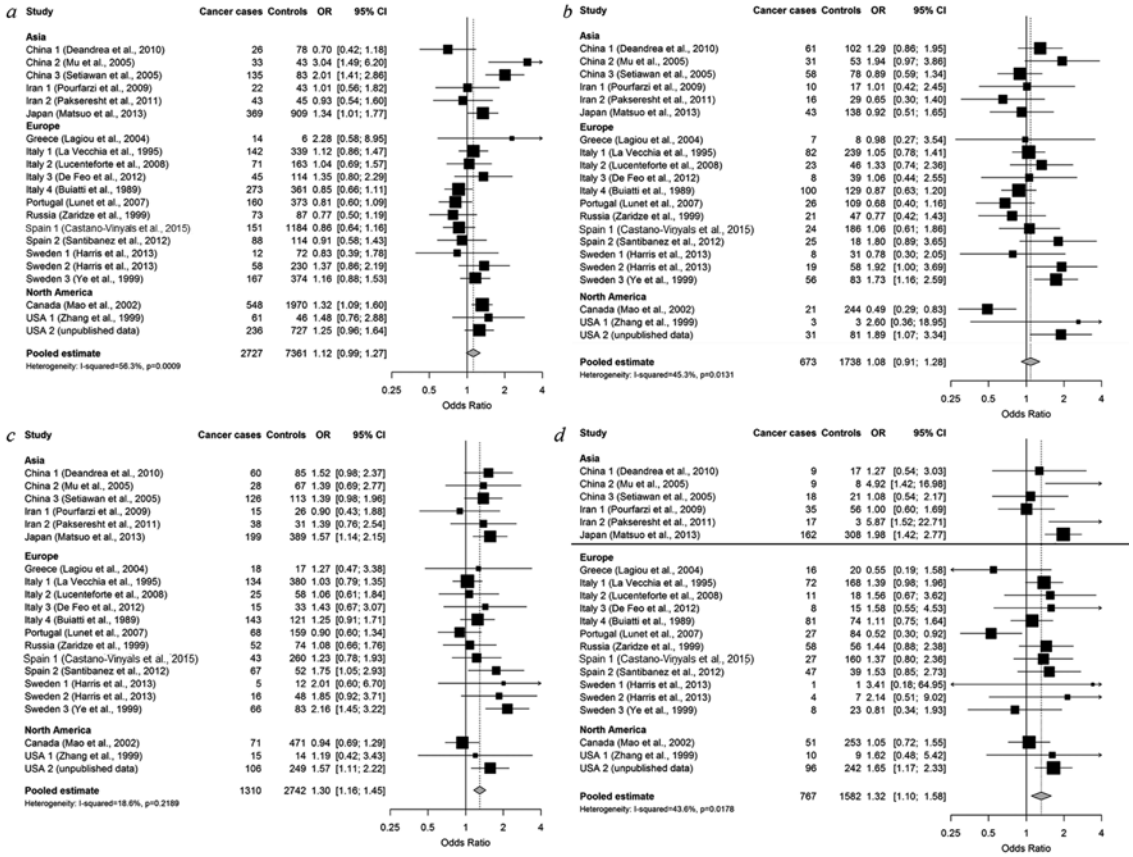

a
Study
Cancer cases
Controls
OR
95% CI
Asia
China 1 (Deandrea et al., 2010) 26 78 0.70 [0.42; 1.18]
China 2 (Mu et al., 2005) 33 43 3.04 [1.49; 6.20]
China 3 (Setiawan et al., 2005) 135 83 2.01 [1.41; 2.86]
Iran 1 (Pourfarzi et al., 2009) 22 43 1.01 [0.56; 1.82]
Iran 2 (Pakseresht et al., 2011) 43 45 0.93 [0.54; 1.60]
Japan (Matsuo et al., 2013) 369 909 1.34 [1.01; 1.77]
Europe
Greece (Lagiou et al., 2004) 14 6 2.28 [0.58; 8.95]
Italy 1 (La Vecchia et al., 1995) 142 339 1.12 [0.86; 1.47]
Italy 2 (Lucenteforte et al., 2008) 71 163 1.04 [0.69; 1.57]
Italy 3 (De Feo et al., 2012) 45 114 1.35 [0.80; 2.29]
Italy 4 (Buiatti et al., 1989) 273 361 0.85 [0.66; 1.11]
Portugal (Lunet et al., 2007) 160 373 0.81 [0.60; 1.09]
Russia (Zaridze et al., 1999) 73 87 0.77 [0.50; 1.19]
Spain 1 (Castano-Vinyals et al., 2015) 151 1184 0.86 [0.64; 1.16]
Spain 2 (Santibanez et al., 2012) 88 114 0.91 [0.58; 1.43]
Sweden 1 (Harris et al., 2013) 12 72 0.83 [0.39; 1.78]
Sweden 2 (Harris et al., 2013) 58 230 1.37 [0.86; 2.19]
Sweden 3 (Ye et al., 1999) 167 374 1.16 [0.88; 1.53]
North America
Canada (Mao et al., 2002) 548 1970 1.32 [1.09; 1.60]
USA 1 (Zhang et al., 1999) 61 46 1.48 [0.76; 2.88]
USA 2 (unpublished data) 236 727 1.25 [0.96; 1.64]
Pooled estimate 2727 7361 1.12 [0.99; 1.27]
Heterogeneity: I-squared=56.3%, p=0.0009
0.25 0.5 1 2 4
Odds Ratio
b
Study
Cancer cases
Controls
OR
95% CI
Asia
China 1 (Deandrea et al., 2010) 61 102 1.29 [0.86; 1.95]
China 2 (Mu et al., 2005) 31 53 1.94 [0.97; 3.86]
China 3 (Setiawan et al., 2005) 58 78 0.89 [0.59; 1.34]
Iran 1 (Pourfarzi et al., 2009) 10 17 1.01 [0.42; 2.45]
Iran 2 (Pakseresht et al., 2011) 16 29 0.65 [0.30; 1.40]
Japan (Matsuo et al., 2013) 43 138 0.92 [0.51; 1.65]
Europe
Greece (Lagiou et al., 2004) 7 8 0.98 [0.27; 3.54]
Italy 1 (La Vecchia et al., 1995) 82 239 1.05 [0.78; 1.41]
Italy 2 (Lucenteforte et al., 2008) 23 46 1.33 [0.74; 2.36]
Italy 3 (De Feo et al., 2012) 8 39 1.06 [0.44; 2.55]
Italy 4 (Buiatti et al., 1989) 100 129 0.87 [0.63; 1.20]
Portugal (Lunet et al., 2007) 26 109 0.68 [0.40; 1.16]
Russia (Zaridze et al., 1999) 21 47 0.77 [0.42; 1.43]
Spain 1 (Castano-Vinyals et al., 2015) 24 186 1.06 [0.61; 1.86]
Spain 2 (Santibanez et al., 2012) 25 18 1.80 [0.89; 3.65]
Sweden 1 (Harris et al., 2013) 8 31 0.78 [0.30; 2.05]
Sweden 2 (Harris et al., 2013) 19 58 1.92 [1.00; 3.69]
Sweden 3 (Ye et al., 1999) 56 83 1.73 [1.16; 2.59]
North America
Canada (Mao et al., 2002) 21 244 0.49 [0.29; 0.83]
USA 1 (Zhang et al., 1999) 3 3 2.60 [0.36; 18.95]
USA 2 (unpublished data) 31 81 1.89 [1.07; 3.34]
Pooled estimate 673 1738 1.08 [0.91; 1.28]
Heterogeneity: I-squared=45.3%, p=0.0131
0.25 0.5 1 2 4
Odds Ratio
c
Study
Cancer cases
Controls
OR
95% CI
Asia
China 1 (Deandrea et al., 2010) 60 85 1.52 [0.98; 2.37]
China 2 (Mu et al., 2005) 28 67 1.39 [0.69; 2.77]
China 3 (Setiawan et al., 2005) 126 113 1.39 [0.98; 1.96]
Iran 1 (Pourfarzi et al., 2009) 15 26 0.90 [0.43; 1.88]
Iran 2 (Pakseresht et al., 2011) 38 31 1.39 [0.76; 2.54]
Japan (Matsuo et al., 2013) 199 389 1.57 [1.14; 2.15]
Europe
Greece (Lagiou et al., 2004) 18 17 1.27 [0.47; 3.38]
Italy 1 (La Vecchia et al., 1995) 134 380 1.03 [0.79; 1.35]
Italy 2 (Lucenteforte et al., 2008) 25 58 1.06 [0.61; 1.84]
Italy 3 (De Feo et al., 2012) 15 33 1.43 [0.67; 3.07]
Italy 4 (Buiatti et al., 1989) 143 121 1.25 [0.91; 1.71]
Portugal (Lunet et al., 2007) 68 159 0.90 [0.60; 1.34]
Russia (Zaridze et al., 1999) 52 74 1.08 [0.66; 1.76]
Spain 1 (Castano-Vinyals et al., 2015) 43 260 1.23 [0.78; 1.93]
Spain 2 (Santibanez et al., 2012) 67 52 1.75 [1.05; 2.93]
Sweden 1 (Harris et al., 2013) 5 12 2.01 [0.60; 6.70]
Sweden 2 (Harris et al., 2013) 16 48 1.85 [0.92; 3.71]
Sweden 3 (Ye et al., 1999) 66 83 2.16 [1.45; 3.22]
North America
Canada (Mao et al., 2002) 71 471 0.94 [0.69; 1.29]
USA 1 (Zhang et al., 1999) 15 14 1.19 [0.42; 3.43]
USA 2 (unpublished data) 106 249 1.57 [1.11; 2.22]
Pooled estimate 1310 2742 1.30 [1.16; 1.45]
Heterogeneity: I-squared=18.6%, p=0.2189
0.25 0.5 1 2 4
Odds Ratio
d
Study
Cancer cases
Controls
OR
95% CI
Asia
China 1 (Deandrea et al., 2010) 9 17 1.27 [0.54; 3.03]
China 2 (Mu et al., 2005) 9 8 4.92 [1.42; 16.98]
China 3 (Setiawan et al., 2005) 18 21 1.08 [0.54; 2.17]
Iran 1 (Pourfarzi et al., 2009) 35 56 1.00 [0.60; 1.69]
Iran 2 (Pakseresht et al., 2011) 17 3 5.87 [1.52; 22.71]
Japan (Matsuo et al., 2013) 162 308 1.98 [1.42; 2.77]
Europe
Greece (Lagiou et al., 2004) 16 20 0.55 [0.19; 1.58]
Italy 1 (La Vecchia et al., 1995) 72 168 1.39 [0.98; 1.96]
Italy 2 (Lucenteforte et al., 2008) 11 18 1.56 [0.67; 3.62]
Italy 3 (De Feo et al., 2012) 8 15 1.58 [0.55; 4.53]
Italy 4 (Buiatti et al., 1989) 81 74 1.11 [0.75; 1.64]
Portugal (Lunet et al., 2007) 27 84 0.52 [0.30; 0.92]
Russia (Zaridze et al., 1999) 58 56 1.44 [0.88; 2.38]
Spain 1 (Castano-Vinyals et al., 2015) 27 160 1.37 [0.80; 2.36]
Spain 2 (Santibanez et al., 2012) 47 39 1.53 [0.85; 2.73]
Sweden 1 (Harris et al., 2013) 1 1 3.41 [0.18; 64.95]
Sweden 2 (Harris et al., 2013) 4 7 2.14 [0.51; 9.02]
Sweden 3 (Ye et al., 1999) 8 23 0.81 [0.34; 1.93]
North America
Canada (Mao et al., 2002) 51 253 1.05 [0.72; 1.55]
USA 1 (Zhang et al., 1999) 10 9 1.62 [0.48; 5.42]
USA 2 (unpublished data) 96 242 1.65 [1.17; 2.33]
Pooled estimate 767 1582 1.32 [1.10; 1.58]
Heterogeneity: I-squared=43.6%, p=0.0178
0.25 0.5 1 2 4
Odds Ratio

Figure 3

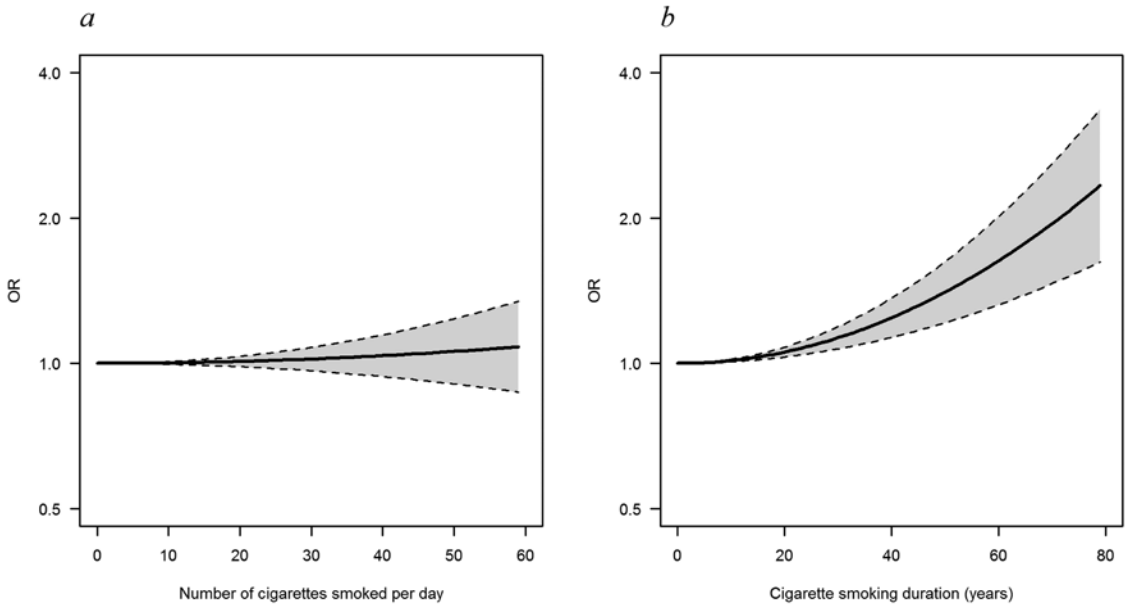
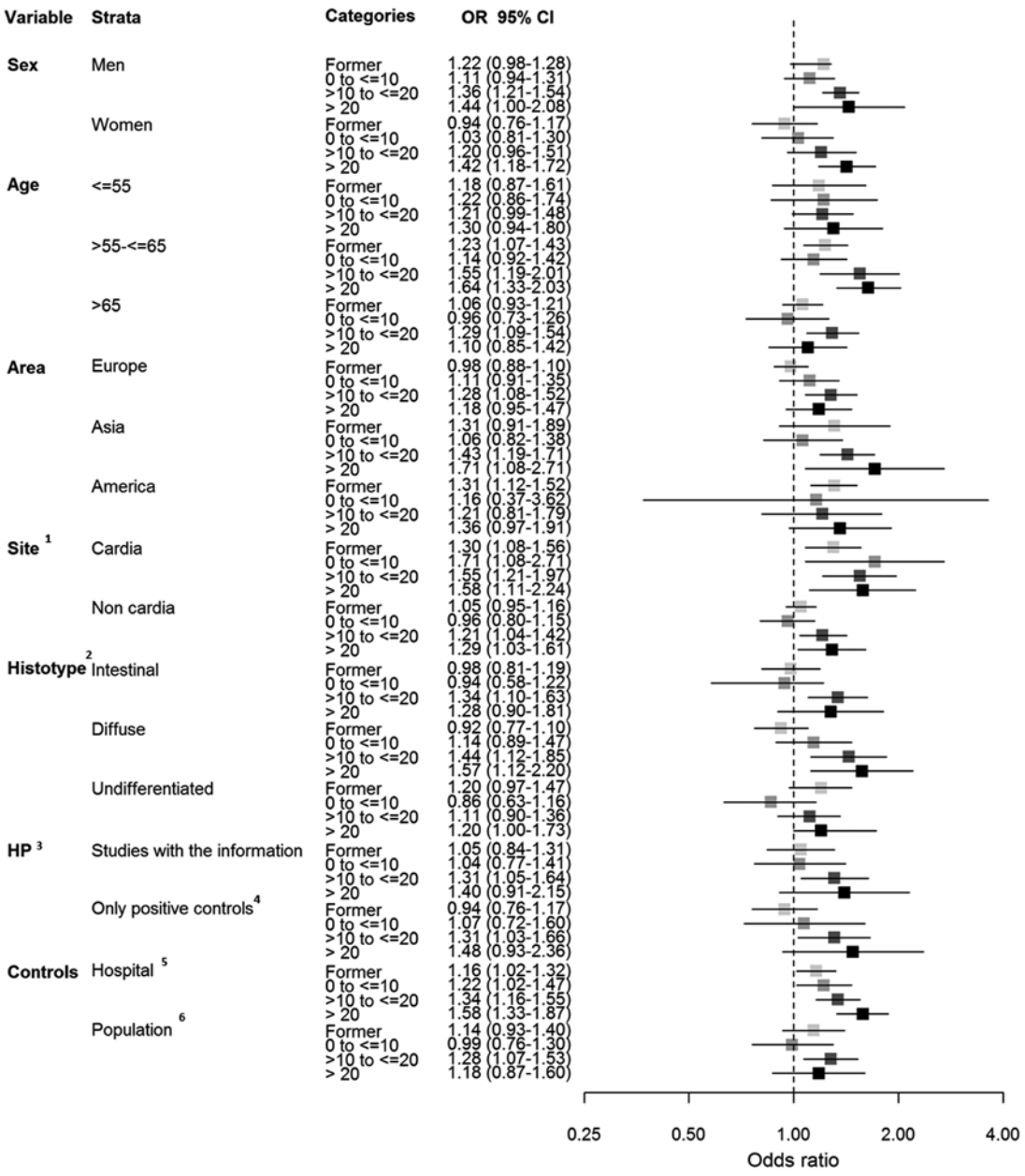

a
b
OR
4.0
2.0
1.0
0.5
0
10
20
30
40
50
60
Number of cigarettes smoked per day
0
20
40
60
80
Cigarette smoking duration (years)

Figure 4


Variable
Strata
Categories
OR 95% CI
Sex
Men
Former 1.22 (0.98-1.28)
0 to <=10 1.11 (0.94-1.31)
>10 to <=20 1.36 (1.21-1.54)
> 20 1.44 (1.00-2.08)
Women
Former 0.94 (0.76-1.17)
0 to <=10 1.03 (0.81-1.30)
>10 to <=20 1.20 (0.96-1.51)
> 20 1.42 (1.18-1.72)
Age
<=55
Former 1.18 (0.87-1.61)
0 to <=10 1.22 (0.86-1.74)
>10 to <=20 1.21 (0.99-1.48)
> 20 1.30 (0.94-1.80)
>55-<=65
Former 1.23 (1.07-1.43)
0 to <=10 1.14 (0.92-1.42)
>10 to <=20 1.55 (1.19-2.01)
> 20 1.64 (1.33-2.03)
>65
Former 1.06 (0.93-1.21)
0 to <=10 0.96 (0.73-1.26)
>10 to <=20 1.29 (1.09-1.54)
> 20 1.10 (0.85-1.42)
Area
Europe
Former 0.98 (0.88-1.10)
0 to <=10 1.11 (0.91-1.35)
>10 to <=20 1.28 (1.08-1.52)
> 20 1.18 (0.95-1.47)
Asia
Former 1.31 (0.91-1.89)
0 to <=10 1.06 (0.82-1.38)
>10 to <=20 1.43 (1.19-1.71)
> 20 1.71 (1.08-2.71)
America
Former 1.31 (1.12-1.52)
0 to <=10 1.16 (0.37-3.62)
>10 to <=20 1.21 (0.81-1.79)
> 20 1.36 (0.97-1.91)
Site [1]
Cardia
Former 1.30 (1.08-1.56)
0 to <=10 1.71 (1.08-2.71)
>10 to <=20 1.55 (1.21-1.97)
> 20 1.58 (1.11-2.24)
Non cardia
Former 1.05 (0.95-1.16)
0 to <=10 0.96 (0.80-1.15)
>10 to <=20 1.21 (1.04-1.42)
> 20 1.29 (1.03-1.61)
Histotype [2]
Intestinal
Former 0.98 (0.81-1.19)
0 to <=10 0.94 (0.58-1.22)
>10 to <=20 1.34 (1.10-1.63)
> 20 1.28 (0.90-1.81)
Diffuse
Former 0.92 (0.77-1.10)
0 to <=10 1.14 (0.89-1.47)
>10 to <=20 1.44 (1.12-1.85)
> 20 1.57 (1.12-2.20)
Undifferentiated
Former 1.20 (0.97-1.47)
0 to <=10 0.86 (0.63-1.16)
>10 to <=20 1.11 (0.90-1.36)
> 20 1.20 (1.00-1.73)
HP [3]
Studies with the information
Former 1.05 (0.84-1.31)
0 to <=10 1.04 (0.77-1.41)
>10 to <=20 1.31 (1.05-1.64)
> 20 1.40 (0.91-2.15)
Only positive controls [4]
Former 0.94 (0.76-1.17)
0 to <=10 1.07 (0.72-1.60)
>10 to <=20 1.31 (1.03-1.66)
> 20 1.48 (0.93-2.36)
Controls
Hospital [5]
Former 1.16 (1.02-1.32)
0 to <=10 1.22 (1.02-1.47)
>10 to <=20 1.34 (1.16-1.55)
> 20 1.58 (1.33-1.87)
Population [6]
Former 1.14 (0.93-1.40)
0 to <=10 0.99 (0.76-1.30)
>10 to <=20 1.28 (1.07-1.53)
> 20 1.18 (0.87-1.60)
0.25
0.50
1.00
2.00
4.00
Odds ratio