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

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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 the risk of gastric cancer 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 with 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 noncardia gastric cancer. Risks were similar when considering only studies with information on *Helicobacter pylori* infection and comparing all cases to *H. pylori* + controls only. This study provides the most precise estimate of the detrimental effect of cigarette smoking on the risk of gastric cancer on the basis of individual data, including the relationship with dose and duration, and the decrease in risk following stopping smoking. *European Journal of Cancer Prevention* 27:124–133 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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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 the risk of gastric cancer among smokers, although quantification of the dose–response relations remains imprecise.

The 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 noncardia 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 generally been found in former compared with current smokers, and the risk seems to decrease with increasing years since stopping smoking, although this 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 carried out an individual participant data meta-analysis of studies participating in 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 and 3486 women) and 26 145 controls (15 600 men and 10 545 women) from Greece (Lagiou *et al.*, 2004), Italy (four 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 (two studies) (Santibanez *et al.*, 2012; Castano-Vinyals *et al.*, 2015), Sweden (three studies, two of which were nested in cohort studies) (Ye *et al.*, 1999; Harris *et al.*, 2013), China (four studies) (Setiawan *et al.*, 2000, 2005; Mu *et al.*, 2005; Deandrea *et al.*, 2010), Iran (three studies) (Derakhshan *et al.*, 2008; Pourfarzi *et al.*, 2009; Pakseresht *et al.*, 2011), Japan (Matsuo *et al.*, 2013), Canada (Mao *et al.*, 2002), and the USA (two studies) (Zhang *et al.*, 1999). Detailed information on the aims and methods of the 'StoP Project' has been provided elsewhere (Pelucchi *et al.*, 2015).

The principal investigators of participating studies were asked to provide information on 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 prespecified 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, independent 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 – that is, cigars and pipes, were considered in a separate category. Two studies (Setiawan *et al.*, 2000; Derakhshan *et al.*, 2008) providing information only on lifetime cigarette status (ever, never) 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 four 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% confidence intervals (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, others), alcohol drinking (never, low: ≤ 12 g/day, intermediate: >12 to ≤ 47 g/day, high: >47 g/day), consumption of fruit and vegetables (study-specific tertiles), and study center (for multicentric studies). The list of study-specific confounders is presented in Supplementary Table 1 (Supplemental digital content 1, *http://links.lww.com/EJCP/A94*).

In the second stage, summary (pooled) effect 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(OR) 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 – that is, 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 carried out analyses stratified by age (≤55, >55 to ≤65, >65 years), sex, geographic area (Europe, Asia, America), cancer site (cardia, noncardia), cancer histotype (intestinal, diffuse, undifferentiated), and type of controls (hospital controls, population controls; controls from two nested case–control studies were considered together with the latter).

We also evaluated the influence of *Helicobacter 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 those obtained using only *H. pylori*-positive controls (assuming that 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 estimates (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 – that is, the one minimizing the model deviance, was selected when the best-fitting model was nonlinear (Royston *et al.*, 1999).

Results

Table 1 shows the distribution of cases and controls by study, sex, age, and major selected potential confounding factors only for a descriptive purpose. Cases were older than controls [age (mean ± SD): 63 ± 11 vs. 60 ± 13, respectively] and had a lower social class. Overall, 8.6% of cases reported a history of stomach cancer among first-degree relatives and 11.2% reported consumption of four or more drinks/day of alcoholic beverages (i.e. >47 g/day of ethanol).

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

The pooled ORs of gastric cancer according to cigarette smoking habits are shown 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

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 [*N* (%)]	Controls [*N* (%)]
Total	10 290	26 145
Study center (reference)		
Europe	5079 (49.4)	12 664 (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)	15 600 (59.7)
Female	3486 (33.9)	10 545 (40.3)
Age		
<40	355 (3.4)	1917 (7.3)
40–44	362 (3.5)	1542 (5.9)
45–49	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)
70–74	1864 (18.1)	3857 (14.8)
≥75	1286 (12.5)	2673 (10.2)
Social class[a]		
Low	5416 (52.6)	10 625 (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[b]		
No	5139 (49.9)	13 092 (50.1)
Yes	885 (8.6)	1287 (4.9)
Missing	4266 (41.5)	11 766 (45.0)
Vegetables and fruit intake[c]		
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 (g/day)[d]		
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)

[a]No information available for study Iran 3 (Derakhshan *et al.*, 2008).
[b]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).
[c]No information available for studies USA 1 (Zhang *et al.*, 1999), China 4 (Setiawan *et al.*, 2000) and Iran 3 (Derakhshan *et al.*, 2008).
[d]Alcohol drinking was not available in the category of consumption for studies Iran 2 (Pakseresht *et al.*, 2011), China 3 (Setiawan *et al.*, 2005), Sweden 3 (Ye *et al.*, 1999), China 4 (Setiawan *et al.*, 2000) and Iran 3 (Derakhshan *et al.*, 2008).

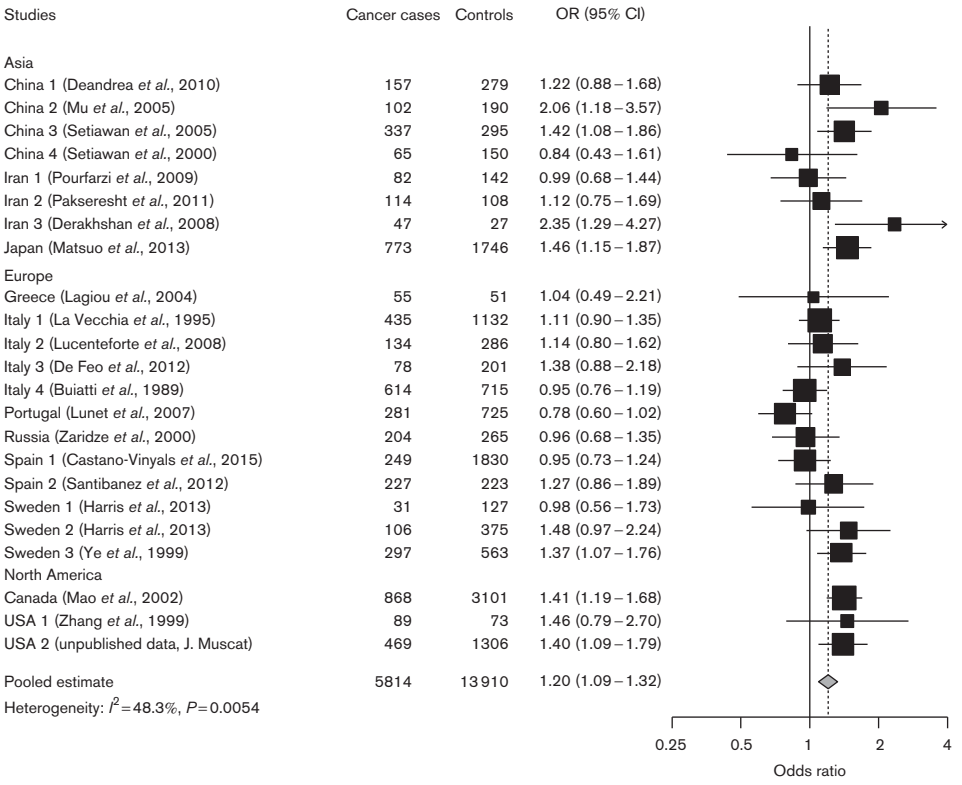
cigarette smokers, and 1.25 (95% CI: 1.11–1.40) for current smokers compared with never smokers. Among current smokers, the risk increased with the number of cigarettes smoked per day. Compared with never smokers, ORs were 1.08 (95% CI: 0.91–1.28) for 1–10 cigarettes per day, 1.30 (95% CI: 1.16–1.45) for 11–20 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 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 31–40 years of smoking, and 1.33 (95% CI: 1.14–1.54) for more than 40 years of smoking compared with never smokers. A significant decreasing trend in risk was found with increasing time since stopping cigarette smoking ($P < 0.01$), taking current smokers as a reference group.

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

Figure 3 shows the modeled relation between smoking intensity (a) and duration (b), considered as continuous variables, and gastric cancer risk. For both variables, the best-fitting model was the one with powers $P_1 = -2$ and $P_2 = 2$ – that is, $\log(\mathrm{OR}) = \beta_1 X^{-2} + \beta_2 X^2$. The estimated regression coefficients were $\beta_1 = -0.00002$ and $\beta_2 = 0.000023$ for smoking intensity and $\beta_1 = -1.46\mathrm{E}-06$ and $\beta_2 = 0.000136$ for duration. Overall, duration appeared to have a somewhat stronger effect on risk than intensity. These graphs suggest that the intensity–risk and duration–risk relationships have a strong nonlinear component ($P < 0.001$).

Stratified analyses according to smoking intensity are shown in Fig. 4 and Supplementary Table 2 (Supplemental digital content 2, *http://links.lww.com/EJCP/A95*). 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 patients aged 56–65 years (OR = 1.64, 95% CI: 1.33–2.03) and in studies carried out 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 noncardia 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,

Fig. 1



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

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

	Cases [*N* (%)]	Controls [*N* (%)]	OR (95% CI)[a]
Total	10 290	26 145	–
Cigarette smoking status			
Never smoker	4261 (41.4)	11 742 (44.9)	1
Ever cigarette smoker	5814 (56.5)	13 910 (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[b]	10 039	25 595	–
Cigarette smoking status			
Never smoker	4122 (41.1)	11 369 (44.4)	1
Ever cigarette smoker	5510 (54.9)	13 539 (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)[c]			
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 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 for trend			<0.0001
Total[d]	7657	18 222	–
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 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

CI, confidence interval; OR, odds ratio.

[a]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.

[b]Information on former/current smoking status was not available for studies China 4 (Setiawan *et al.*, 2000) and Iran 3 (Derakhshan *et al.*, 2008).

[c]Current smokers only.

[d]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).

respectively). For patients reporting high intensity of cigarette smoking, the ORs were 1.58 for cardia (95% CI: 1.11–2.24) and 1.29 for noncardia (95% CI: 1.03–1.61) gastric cancer, and in terms of histotype, 1.28 (95% CI: 0.90–1.81) for intestinal-type and 1.57 (95% CI: 1.12–2.20) for diffuse-type gastric cancer. Effects of cigarette smoking on the risk of gastric cancer 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).

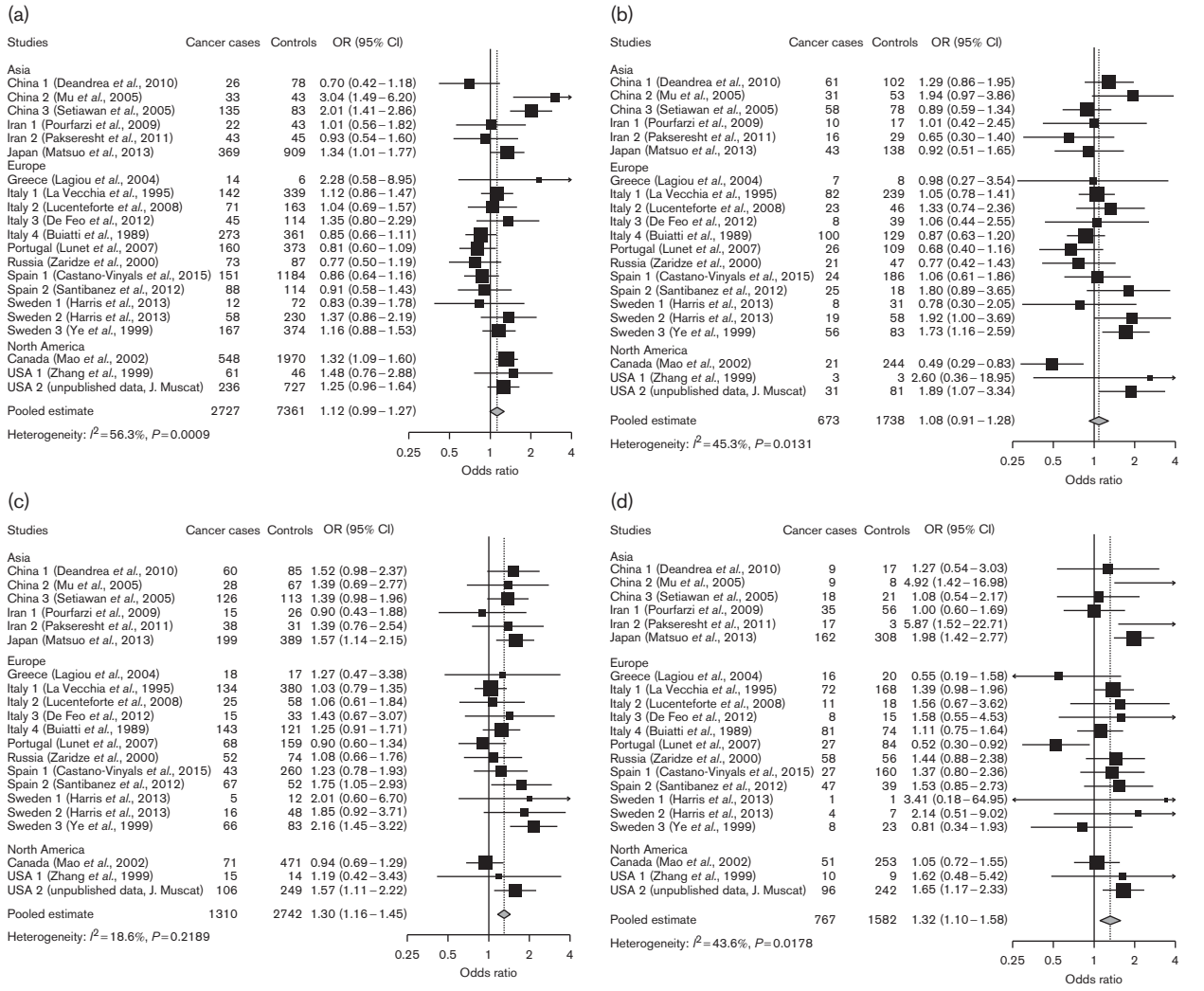
Stratified analyses on smoking duration according to sex, age, geographic area, cancer site, cancer histotype, source of controls, and *H. pylori* infection are shown in Supplementary Table 3 (Supplemental digital content 3, *http://links.lww.com/EJCP/A96*). When considering long-term smokers (i.e. >40 years of smoking), the risks appeared to be higher in gastric cardia (OR = 1.78, 95% CI: 1.44–2.19) than in noncardia (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 the risk of gastric cancer. This is the largest individual participant analysis on gastric neoplasia, 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 increased significantly 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, compared with never smokers. The increase in risk was steeper for duration than for dose. The risk decreased 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 on the basis of 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 overestimation of the risk in the published literature. In fact, only about one-third of the studies included in this pooled analysis were present

Fig. 2



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

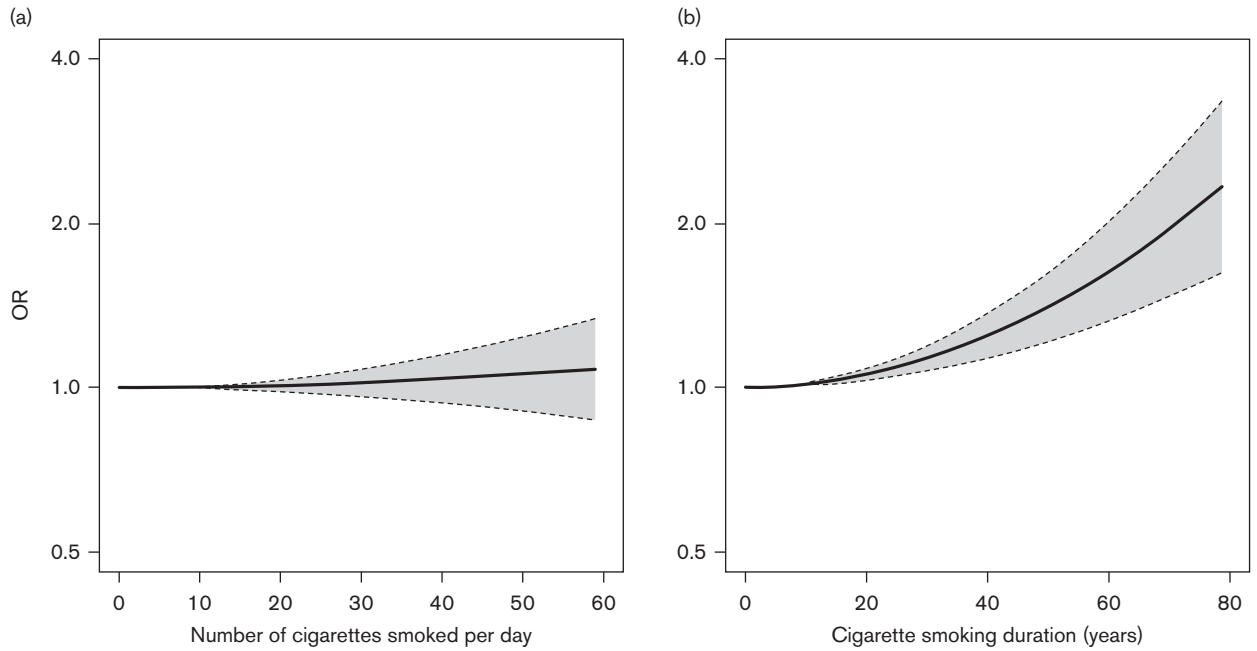
in previous meta-analyses of case–control (La Torre *et al.*, 2009) or cohort studies (Ladeiras-Lopes *et al.*, 2008).

In terms of 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 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 study (Nomura *et al.*, 2012). Although the association of gastric cancer with smoking has long been recognized, this study confirms that the risk is modest even at high doses, despite 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 has been shown for lung cancer.

An interesting finding of our study is the lower gastric cancer risk for former smokers compared with current smokers, particularly, 10 years or more 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

Fig. 3



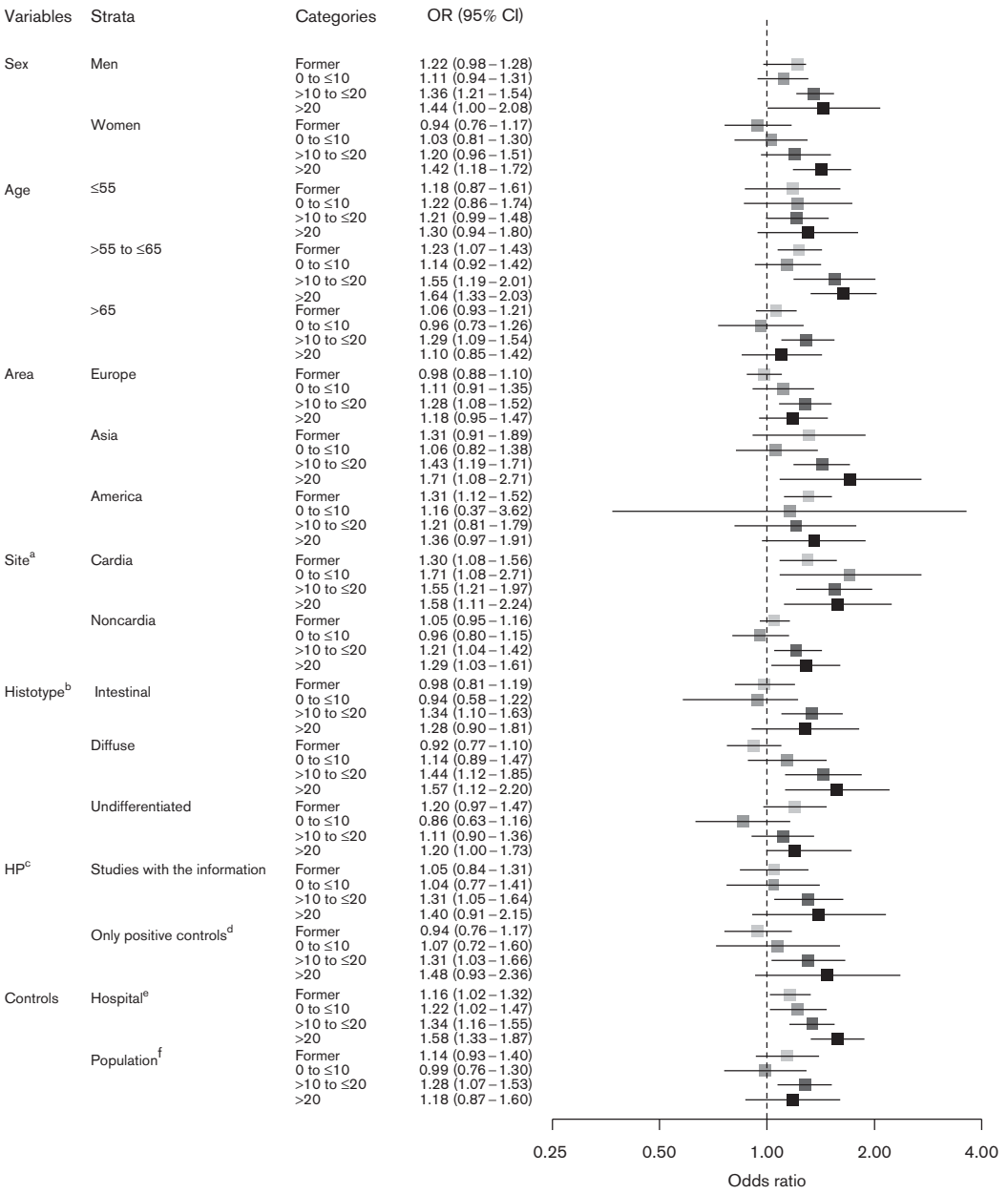
Relation between intensity (a) or duration of cigarette smoking (b), and risk of gastric cancer (odds ratios, ORs, and corresponding 95% confidence intervals) according to the best-fitting fractional polynomial model, that is, the one with powers $P_1 = -2$ and $P_2 = 2$, in the Stomach cancer Pooling (StoP) Project consortium.

noncardia 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 with never smokers (Tramacere *et al.*, 2011). A differential role of smoking [besides *H. pylori* (Kamangar *et al.*, 2006)] in the etiology of different gastric cancer subsites has also been hypothesized to contribute toward the diverging trends in the risk of gastric cardia and noncardia cancers over the last decades (Gonzalez *et al.*, 2003). In this investigation, although 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 noncardia 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 noncardia 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 noncardia cancer, suggesting underlying differences in the 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 associated significantly with the development of precursor lesion of gastric cancer – that is, 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 nonsmokers (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 susceptibility in the relation between smoking and gastric cancer (Agudo *et al.*, 2006; Lee *et al.*, 2006; Boccia *et al.*, 2007). Furthermore, the hypermethylation of the *CDH1* gene was observed preferentially in gastric tumors from smokers rather than nonsmokers (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–risk and temporal factors–risk relationships and, among former smokers, the pattern of risk with time since stopping. The individual level approach has several advantages compared with study-level meta-analyses, specifically the availability of detailed and uniform information on important covariates (Ioannidis *et al.*, 2013). For instance, we could investigate the confounding effect of *H. pylori* infection by restricting the analysis to controls positive for *H. pylori* infection (all cases were

Fig. 4



Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to the intensity of cigarette smoking in strata of sex, age, geographic area, cancer site, cancer histotype, *Helicobacter pylori* infection, and control recruitment in the Stomach cancer Pooling (StoP) Project consortium. (a) Considered studies: Italy 1 (La Vecchia *et al.*, 1995), Italy 2 (Lucenteforte *et al.*, 2008), Italy 3 (De Feo *et al.*, 2012), Italy 4 (Buiatti *et al.*, 1989), Canada (Mao *et al.*, 2002), Russia (Zaridze *et al.*, 2000), Iran 1 (Pourfarzi *et al.*, 2009), Iran 2 (Pakseresht *et al.*, 2011), USA 1 (Zhang *et al.*, 1999), Japan (Matsuo *et al.*, 2013), USA 2 (unpublished data, J Muscat), Portugal (Lunet *et al.*, 2007), Sweden 1 (Harris *et al.*, 2013), Sweden 2 (Harris *et al.*, 2013), Spain 1 (Castano-Vinyals *et al.*, 2015), Sweden 3 (Ye *et al.*, 1999), Spain 2 (Santibanez *et al.*, 2012). (b) Considered studies: Italy 2 (Lucenteforte *et al.*, 2008), Italy 3 (De Feo *et al.*, 2012), Italy 4 (Buiatti *et al.*, 1989), Canada (Mao *et al.*, 2002), Russia (Zaridze *et al.*, 2000), Iran 1 (Pourfarzi *et al.*, 2009), Iran 2 (Pakseresht *et al.*, 2011), USA 1 (Zhang *et al.*, 1999), Japan (Matsuo *et al.*, 2013), Portugal (Lunet *et al.*, 2007), Spain 1 (Castano-Vinyals *et al.*, 2015), Sweden 3 (Ye *et al.*, 1999), Spain 2 (Santibanez *et al.*, 2012). (c)The studies Italy 3 (De Feo *et al.*, 2012) and Spain 2 (Santibanez *et al.*, 2012) were not considered because no information was available for controls, or controls were all H. pylori negative. Considered studies: China 2 (Mu *et al.*, 2005), Iran 1 (Pourfarzi *et al.*, 2009), Iran 2 (Pakseresht *et al.*, 2011), Japan (Matsuo *et al.*, 2013), Portugal (Lunet *et al.*, 2007), Russia (Zaridze *et al.*, 2000), Spain 1 (Castano-Vinyals *et al.*, 2015), Sweden 3 (Ye *et al.*, 1999). (d)Pooled ORs were computed considering all cases and only controls positive for H. pylori infection. (e) Considered studies: Italy 1 (La Vecchia *et al.*, 1995), China 1 (Deandrea *et al.*, 2010), Italy 2 (Lucenteforte *et al.*, 2008), Italy 3 (De Feo *et al.*, 2012), Greece (Lagiou *et al.*, 2004), USA 1 (Zhang *et al.*, 1999), Japan (Matsuo *et al.*, 2013), USA 2 (unpublished data, J Muscat), Spain 2 (Santibanez *et al.*, 2012). (f) Considered studies: Italy 4, Canada (Johnson), China 2 (Mu *et al.*, 2005), Iran 1 (Pourfarzi *et al.*, 2009), Iran 2 (Pakseresht *et al.*, 2011), China 3 (Setiawan *et al.*, 2005), Portugal (Lunet *et al.*, 2007), Sweden 1 (Harris *et al.*, 2013), Sweden 2 (Harris *et al.*, 2013), Spain 1 (Castano-Vinyals *et al.*, 2015), Sweden 3 (Ye *et al.*, 1999). The Russian study (Zaridze *et al.*, 2000) was not considered in this analysis because it included both hospital and general population controls.

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 considerable 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 could not address the role of such factors, however, as only a minority of studies had available information on the type of cigarette smoked. The association was, if anything, stronger in studies using hospital controls. This is reassuring as 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 with nonsmokers.

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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Conflicts of interest

There are no conflicts of interest.

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