Gastric Cancer (2024) 27:197–209
https://doi.org/10.1007/s10120-023-01459-1

REVIEW ARTICLE

Dose–response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis

Matteo Rota[1] · Irene Possenti[2] · Valeria Valsassina[2] · Claudia Santucci[2,3] · Vincenzo Bagnardi[4] · Giovanni Corrao[5,6] · Cristina Bosetti[2] · Claudia Specchia[1] · Silvano Gallus[2] · Alessandra Lugo[2]

Received: 28 August 2023 / Accepted: 16 December 2023 / Published online: 17 January 2024

Abstract

This study aims at providing an accurate and up-to-date quantification of the dose–response association between cigarette smoking and gastric cancer (GC) risk, overall and by subsite. We conducted a systematic review and meta-analysis of case–control and cohort studies on the association between cigarette smoking and GC risk published up to January 2023. We estimated pooled relative risks (RR) of GC and its subsites according to smoking status, intensity, duration, and time since quitting. Among 271 eligible articles, 205 original studies were included in this meta-analysis. Compared with never smokers, the pooled RR for GC was 1.53 (95% confidence interval; CI 1.44–1.62; $n=92$) for current and 1.30 (95% CI 1.23–1.37; $n=82$) for former smokers. The RR for current compared with never smokers was 2.08 (95% CI 1.66–2.61; $n=21$) for gastric cardia and 1.48 (95% CI 1.33–1.66; $n=8$) for distal stomach cancer. GC risk nonlinearly increased with smoking intensity up to 20 cigarettes/day (RR:1.69; 95% CI 1.55–1.84) and levelled thereafter. GC risk significantly increased linearly with increasing smoking duration (RR: 1.31; 95% CI 1.25–1.37 for 20 years) and significantly decreased linearly with increasing time since quitting (RR: 0.65; 95% CI 0.44–0.95 for 30 years since cessation). The present meta-analysis confirms that cigarette smoking is an independent risk factor for GC, particularly for gastric cardia. GC risk increases with a low number of cigarettes up to 20 cigarettes/day and increases in a dose-dependent manner with smoking duration.

Keywords Gastric cancer · Stomach cancer · Cigarette smoking · Dose–response relationship · Meta-analysis · Helicobacter pylori

✉ Alessandra Lugo
alessandra.lugo@marionegri.it

[1] Department of Molecular and Translational Medicine, Università Degli Studi Di Brescia, Brescia, Italy

[2] Department of Medical Epidemiology, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri 2, 20156 Milan, Italy

[3] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[4] Department of Statistics and Quantitative Methods, Università Degli Studi Di Milano-Bicocca, Milan, Italy

[5] Laboratory of Healthcare Research and Pharmacoepidemiology, Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

[6] National Centre of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy

Introduction

Gastric cancer (GC) is the sixth more frequent neoplasm worldwide, with an estimated incidence rate of 11.1 per 100,000 person-years and a twofold higher incidence in men than in women (15.8 vs. 7.0 per 100,000 person-years) [1]. Although considered a single disease entity, GC can be classified into two major topographical subsites: cardia GC, arising in the area of the stomach adjoining the oesophageal-gastric junction, and non-cardia GC, arising from more distal regions of the stomach [2].

GC is a multi-factorial disease, involving genetic and environmental determinants, with low socioeconomic status, *Helicobacter pylori* (*H. pylori*) infection, and selected dietary factors, as low consumption of fruits and vegetables and high intake of salty and smoked food, being the most recognized risk factors [3]. In the wake of the accumulating evidence on tobacco carcinogenicity from studies conducted since the last half of the past century, in 2012

the International Agency for Research on Cancer (IARC) concluded that there was 'sufficient' evidence of causality between tobacco smoking and GC [4]. Eradication of *H. pylori* infection, better methods of food preservation, and increasing awareness of the importance of a healthy diet contributed to the substantial decline in incidence and mortality rates over the past 50 years [5]. This favourable trend is mainly due to the falling rates of non-cardia GC, as opposite to the rising trend in cardia GC observed in more recent years [3, 4, 6, 7]. Despite that, GC is still the third leading cause of cancer mortality worldwide [1].

Several systematic reviews and meta-analyses conducted over the last decade [8–12], showed that current smokers had an about 60% increased risk of GC as compared with never smokers, the association being stronger in men [11]. However, these meta-analyses included either cohort [11] or case–control studies [8], or focused on selected populations [8–10]. Moreover, they did not comprehensively quantify the dose-risk relationship with smoking intensity, duration, and, for former smokers, time since quitting. Meanwhile, more high-quality epidemiological studies on the issue became available.

Using an innovative approach [13], we aim to provide an accurate and up-to-date quantification of the dose-risk association between cigarette smoking and GC risk, overall and according to cancer subsite.

Methods

The present meta-analysis is part of a series of systematic reviews and meta-analyses on the association between cigarette smoking and secondhand smoke exposure and the risk of cancer [13–16]. This review takes advantage of an innovative methodology to identify original articles, based on a combination of umbrella and traditional reviews [15, 17]. Through the Umbrella Review we identified all meta-analyses, pooled analyses, and reviews on the association between cigarette smoking and GC risk. The original studies published after the most recent and comprehensive review were identified through a traditional review. The study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017063991).

Search strategy

As a first step, we conducted an umbrella review on smoking and the risk of cancer at any site. Through a comprehensive literature search on various databases (PubMed/MEDLINE, Embase, Institute for Scientific Information Web of Science, and the Cochrane Database of Systematic Reviews), we identified all meta-analyses, pooled analyses, and reviews on the association between cigarette smoking and cancer risk published up to October 12 2022. In particular, we identified 20 systematic reviews/meta-analyses [8–12, 18–32] and 16 pooled analyses [33–48] on GC (Supplementary Fig. 1). We also considered two monographs of the IARC on tobacco smoking [4, 49] and one report from the Centers for Disease Control and Prevention [50]. We screened the 39 above-mentioned reports and identified a total of 370 non-duplicate original publications on tobacco smoking and the risk of GC. These articles were screened on the basis of their full text using the eligibility criteria described in the following section, leading to the exclusion of 173 papers (Supplementary Table 1).

In a second step, we carried out a literature search to identify all original studies published between January 2008 (i.e., the publication date of the last and most comprehensive review available on the topic [4]) and January 31 2023. The search string was comprehensive and included combinations of MeSH and text words related to gastric cancer and tobacco or smoking (Supplementary Box 1). After the exclusion of duplicate publications and ineligible articles, and the inclusion of five additional relevant publications identified from other sources, the update of the scientific literature resulted in 133 additional original publications on cigarette smoking and the risk of GC.

Combining original articles identified in the umbrella review (step 1) and in the update of the literature (step 2), a total of 271 non-duplicate publications were identified as eligible (Supplementary Fig. 1).

Eligibility criteria

Studies were included in the present meta-analysis if they satisfied the following eligibility criteria: (i) they were either case–control studies (including nested case–control studies or pooled analyses of case–control studies) or cohort studies (including case-cohort studies or pooled analyses of cohort studies); (ii) they were published as original articles in English; (iii) they provided data on the general population; (iv) they provided information on the association between cigarette smoking and malignant GC risk, either overall or according to topographical subsites (cardia GC and non-cardia GC, including distal or proximal stomach); (v) they reported risk estimates, including risk ratios, odds ratios, hazard ratios or mortality rate ratios—all referred to as relative risk (RR)—for at least one variable among smoking status (current, former and/or ever smoking), intensity, duration, and time since quitting, compared with never or current cigarette smokers, and corresponding 95% confidence intervals (CI), or providing sufficient information to compute them.

Data extraction

For each eligible study, we collected general information on the publication (e.g., first author, year of publication, and journal), study (e.g., country, study name, calendar period, study design, and sample size), the model used for RR estimates (including covariates allowed for), and RRs with the corresponding 95% CIs and, when available, the number of cases and controls (or subjects at risk/person-years for cohort studies) for various exposure categories.

Where necessary, we used the method for pooling non-independent estimates described by Hamling and colleagues [51] to change the reference category or collapse the RRs of two or more categories when the reference group was the same. Where RRs were reported separately for different subsites of GC, we used the method described by Rucker and colleagues [52] to obtain a single RR for overall GC.

Statistical methods

Pooled RRs for current, former, and ever smokers were estimated for GC and, separately, for distal and proximal GC and for gastric cardia, overall and by study design (i.e., cohort and case–control). These estimates were obtained using random-effects meta-analytic models to take into account the heterogeneity of risk estimates [53]. Heterogeneity between studies was assessed using the χ^2 test and inconsistency was measured using the I^2 statistic, which represents the proportion of total variation attributable to between-study variance [54]. We conducted stratified analyses based on various study and population characteristics (study design, cancer subsite, sex, type of control, endpoint, tertiles of number of cases, presence of any adjustment, adjustment or matching for *H. pylori* infection, geographic area, income group, and year of publication). To evaluate publication bias, we examined the funnel plots [55] and applied Egger's test for funnel plot asymmetry [56].

Study quality was assessed by two authors (AL and IP) using the Newcastle–Ottawa Scale (NOS) [77]. NOS score ranges between 0 (poor quality) and 9 (good quality) and consider information on three broad categories: selection (maximum 4 points), comparability (maximum 2 points) and outcome for case–control or exposure for cohort studies (maximum 3 points). In this meta-analysis, high-quality studies were defined as those with NOS scores ≥ 7. To ensure the completeness and comprehensiveness of our study, no low-quality study was excluded from the meta-analysis.

We investigated both linear and nonlinear associations between smoking intensity (for current vs. never smokers), smoking duration (for current vs. never smokers), pack-years (for current vs. never smokers), and time since quitting (for former vs. current smokers), and the log RR of GC. Dose–response relationships between smoking variables and log RR of GC, either linear or not, were evaluated using a one-stage random-effects dose–response model [57]. For each exposure variable, we tested the statistical significance of nonlinear coefficients using the Wald test. In the case of rejection of linearity, the nonlinear relationships were modelled using restricted cubic splines with 3 knots at fixed percentiles of exposure (10%, 50%, and 90%) [15, 58]. For each category, the level of exposure was assigned as the midpoint between the upper and the lower bounds; for open-ended upper categories, the level of exposure was determined as 1.2 times the lower bound [13, 59, 60]. When the number of cases and/or controls in one or more exposure categories was not provided in the original study publication, we estimated the covariance among the log RR by considering the total number of cases and/or controls in the study weighted by the average percent distribution of subjects pooled from all other studies [61].

All statistical analyses were performed using the R-software version 4.2.2 (R Development Core Team, 2017), and, in particular, the "meta" and "dosresmeta" packages [61, 62].

Results

Study selection and description

Among 271 eligible original articles, 66 were excluded because their results were already reported in other publications (Supplementary Table 1). Thus, a total of 205 original articles (129 case–control and 76 cohort studies) met the eligibility criteria and were included in the present meta-analysis (Supplementary Table 2 and Supplementary Table 3). Included studies were published between 1958 and 2022 and described a total of 677,040 GC cases. Ninety-two studies on overall GC provided a measure of the association (or information to derive it) for current smokers, 82 for former smokers, and 164 for ever smokers, as compared with never smokers. Moreover, 62 studies reported RR estimates for smoking intensity (29 among current smokers), 30 for smoking duration (9 among current smokers), 5 for pack-years among current smokers, and 17 for time since quitting. Publications containing data that were partially excluded from the present meta-analysis, with the corresponding reasons of exclusion, are described in Supplementary Table 4. Study-specific quality scores for case–control and cohort studies are showed in Supplementary Table 5 and 6, respectively, with 27 high-quality case–control studies and 37 high-quality cohort studies identified among the 205 included articles.

Quantitative data synthesis

The pooled RR of GC for current compared with never smokers was 1.53 (95% CI 1.44–1.62) overall, 1.57 (95% CI 1.38–1.78) in case–control, and 1.50 (95% CI 1.42–1.59) in cohort studies (Fig. 1). The corresponding estimates for former compared with never smokers were 1.30 (95% CI 1.23–1.37), 1.38 (95% CI 1.23–1.54), and 1.27 (95% CI 1.21–1.33), respectively (Fig. 2). The pooled RR for ever compared with never smokers was 1.53 (95% CI 1.45–1.62), and was significantly higher in case control (RR: 1.63; 95% CI 1.50–1.76) than in cohort (RR: 1.37; 95% CI 1.30–1.44) studies (p-value for heterogeneity between study designs < 0.01; Supplementary Fig. 2). For all pooled estimates, significant between-study heterogeneity was observed.

Compared with never smokers, the RR for cardia GC was 2.08 (95% CI 1.66–2.61; $n = 21$) for current smokers, 1.77 (95% CI 1.51–2.08; $n = 20$) for former smokers, and 1.81 (95% CI 1.55–2.12; $n = 31$) for ever smokers (Table 1 and Supplementary Figs. 3–5). The RR for distal GC was 1.48 (95% CI 1.33–1.66; $n = 8$) for current smokers, 1.28 (95% CI 1.18–1.39; $n = 8$) for former smokers, and 1.49 (95% CI 1.28–1.74; $n = 11$) for ever smokers (Table 1 and Supplementary Figs. 6–8). The RR for proximal GC was 2.38 (95% CI 1.58–3.58; $n = 2$) for current smokers, 0.89 (95% CI 0.44–1.80; $n = 1$) for former, and 1.42 (95% CI 1.04–1.94; $n = 3$) for ever smokers (Table 1).

Possible sources of heterogeneity were investigated through stratified analyses (Table 1). Among current smokers, significant differences have been observed according to geographic area (RRs of GC were 1.79 in studies conducted in North America, 1.42 in those conducted in Europe, 1.48 in those conducted in Asia, 1.58 in those conducted in South America, 1.42 in those conducted in Oceania, and 6.30 in one study conducted in Africa; $p = 0.02$) and income group (RRs were 1.32 for middle/low- and 1.58 for high-income countries; $p < 0.01$). Among former smokers, significant differences were observed according to sex (RRs were 1.13 for women and 1.32 for men; $p = 0.01$). Among ever smokers, significant differences were observed according to sex (RRs were 1.16 for women and 1.43 for men; $p < 0.01$), number of cases (RRs were 1.68 among studies with less than 150 cases, 1.72 among studies with a number of cases between 150 and 399, and 1.36 among studies with more than 399 cases; $p < 0.01$), presence of any adjustment (RRs were 1.88 in studies with crude RR and 1.49 in studies with adjusted RR; $p = 0.03$), adjustment/matching for *H. pylori* (RRs were 1.81 in studies adjusting for *H. pylori* and 1.50 in studies not adjusting for it; $p = 0.02$), and geographic area (RRs of GC were 1.51 in studies conducted in North America, 1.30 in those conducted in Europe, 1.64 in those conducted in Asia, 1.38 in those conducted in South America, 1.47 in those

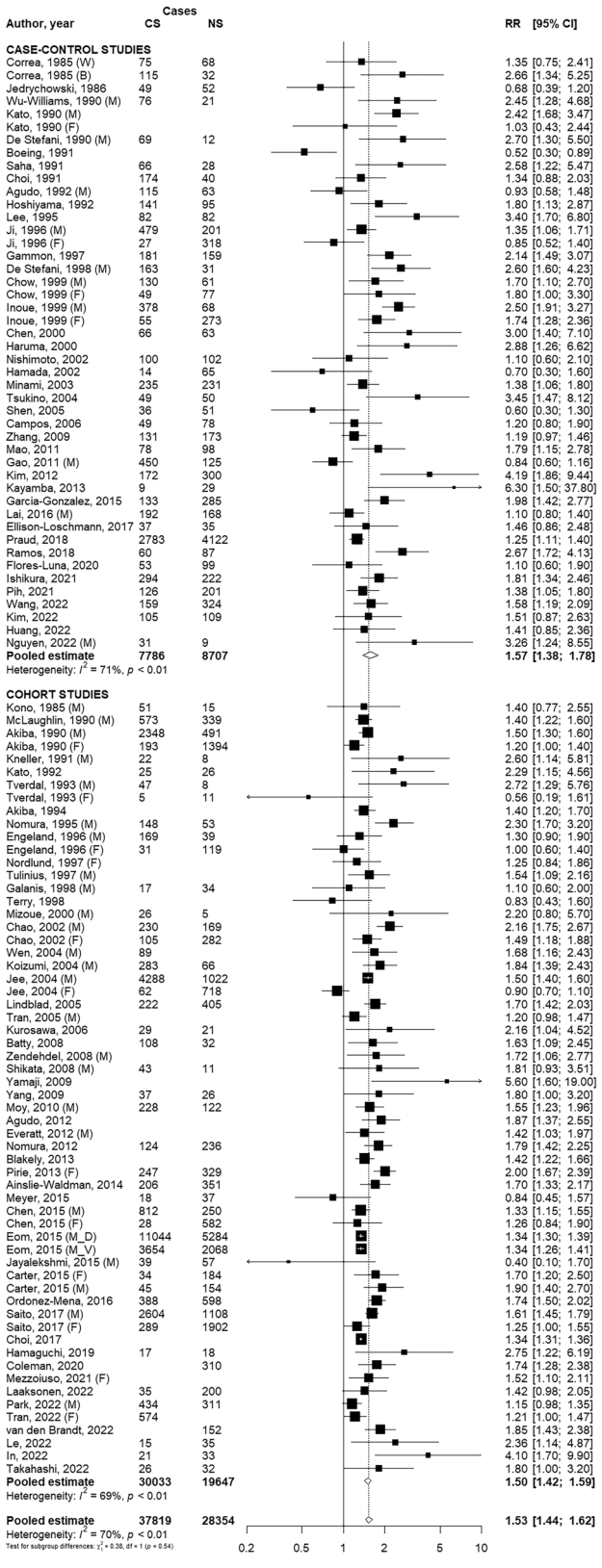

Fig. 1 Forest plot of study-specific and pooled relative risk (RR) of gastric cancer for current cigarette smokers (CS) versus never smokers (NS), by study design. *B* black, *CI* confidence interval, *F* females, *M* males, *M_D* males included in the development cohort, *M_V* males included in the validation cohort, *W* white

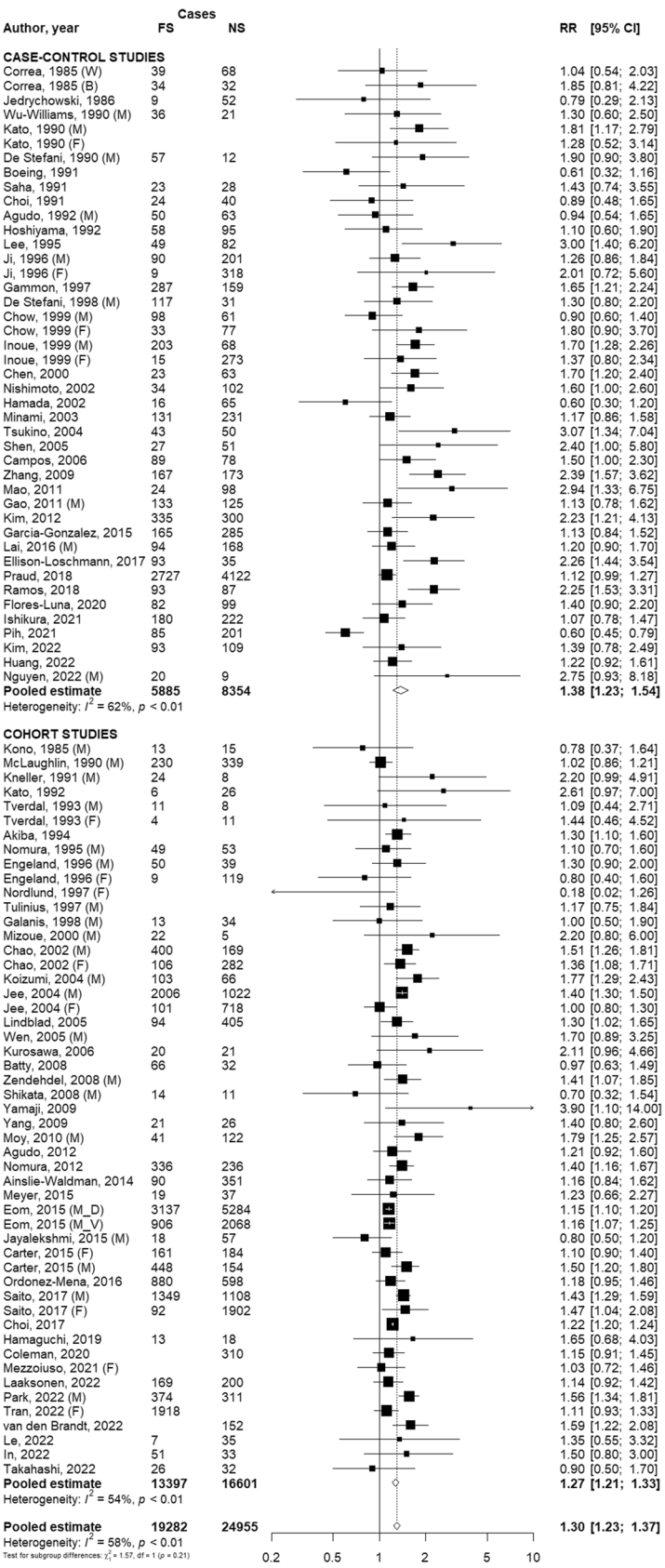

Fig. 2 Forest plot of study-specific and pooled relative risk (RR) of gastric cancer for former cigarette smokers (FS) versus never smokers (NS), by study design. *B* black, *CI* confidence interval, *F* females, *M* males, *M_D* males included in the development cohort, *M_V* males included in the validation cohort, *W* white

Table 1 Pooled relative risk (RR) and corresponding 95% confidence interval (CI) for gastric cancer risk for current, former, and ever cigarette smokers vs. never cigarette smokers, overall and in strata of selected characteristics

Strata	Current smokers				Former smokers				Ever smokers			
	N. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N.* studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N.* studies	Pooled RR (95% CI)	*p*-value*	*p*-value#
Total	92	1.53 (1.44–1.62)	–	< 0.01	82	1.30 (1.23–1.37)	–	< 0.01	164	1.53 (1.45–1.62)	–	< 0.01
Cancer subsite												
Cardia	21	2.08 (1.66–2.61)	–	< 0.01	20	1.77 (1.51–2.08)	–	< 0.01	31	1.81 (1.55–2.12)	–	< 0.01
Distal	8	1.48 (1.33–1.66)		0.14	8	1.28 (1.18–1.39)		0.74	11	1.49 (1.28–1.74)		< 0.01
Proximal	2	2.38 (1.58–3.58)		0.20	1	0.89 (0.44–1.80)		–	3	1.42 (1.04–1.94)		0.21
Sex												
Men	46	1.54 (1.35–1.75)	0.13	< 0.01	43	1.32 (1.24–1.41)	0.01	< 0.01	54	1.43 (1.32–1.55)	< 0.01	< 0.01
Women	21	1.34 (1.18–1.52)		< 0.01	19	1.13 (1.04–1.24)		0.20	27	1.16 (1.08–1.24)		< 0.01
Type of study												
Case–control	41	1.57 (1.38–1.78)	0.54	< 0.01	38	1.38 (1.23–1.54)	0.22	< 0.01	112	1.63 (1.50–1.76)	< 0.01	< 0.01
Cohort	51	1.50 (1.42–1.59)		< 0.01	44	1.27 (1.21–1.33)		< 0.01	52	1.37 (1.30–1.44)		< 0.01
Type of controls[a]												
Hospital	29	1.68 (1.42–1.98)	0.30	< 0.01	27	1.42 (1.23–1.65)	0.73	< 0.01	68	1.75 (1.56–1.95)	0.04	< 0.01
Population	10	1.46 (1.18–1.80)		< 0.01	9	1.37 (1.14–1.64)		0.10	42	1.49 (1.35–1.65)		< 0.01
Endpoint[b]												
Incidence	35	1.47 (1.39–1.55)	0.29	< 0.01	30	1.28 (1.21–1.35)	0.95	< 0.01	38	1.38 (1.31–1.45)	0.83	< 0.01
Mortality	19	1.56 (1.41–1.73)		< 0.01	17	1.28 (1.18–1.39)		0.05	23	1.40 (1.27–1.53)		< 0.01
Number of cases[c]												
< 150	28	1.67 (1.32–2.10)	0.19	< 0.01	25	1.31 (1.09–1.58)	0.27	0.03	55	1.68 (1.47–1.92)	< 0.01	< 0.01
150–399	21	1.65 (1.46–1.87)		0.01	20	1.43 (1.24–1.65)		< 0.01	58	1.72 (1.55–1.90)		< 0.01
≥ 400	42	1.48 (1.39–1.57)		< 0.01	36	1.27 (1.20–1.34)		< 0.01	51	1.36 (1.28–1.44)		< 0.01

Table 1 (continued)

Strata	Current smokers				Former smokers				Ever smokers			
	N. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N*. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N*. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#
Any adjustment												
Crude	7	1.83 (1.35–2.48)	0.24	0.03	5	1.54 (1.03–2.28)	0.40	0.02	21	1.88 (1.54–2.29)	0.03	< 0.01
Adjusted	85	1.52 (1.43–1.61)		< 0.01	88	1.29 (1.23–1.37)		< 0.01	143	1.49 (1.41–1.58)		< 0.01
Adjustment/matching for Helicobacter Pylori												
No	81	1.50 (1.42–1.60)	0.06	< 0.01	72	1.30 (1.24–1.37)	1.00	< 0.01	139	1.50 (1.41–1.59)	0.02	< 0.01
Yes	11	1.92 (1.50–2.45)		0.03	10	1.30 (0.97–1.75)		< 0.01	25	1.81 (1.55–2.11)		< 0.01
Study quality												
Low (NOS < 7)	54	1.57 (1.43–1.73)	0.35	< 0.01	49	1.32 (1.21–1.45)	0.81	< 0.01	120	1.49 (1.39–1.60)	0.85	< 0.01
High (NOS ≥ 7)	38	1.52 (1.41–1.63)		< 0.01	33	1.31 (1.23–1.38)		< 0.01	44	1.50 (1.39–1.63)		< 0.01
Geographic area[d]												
North America	13	1.79 (1.60–2.02)	0.02	0.01	13	1.30 (1.18–1.43)	0.31	0.08	20	1.51 (1.40–1.62)	0.01	< 0.01
Europe	20	1.42 (1.22–1.64)		< 0.01	17	1.19 (1.08–1.32)		0.31	22	1.30 (1.15–1.47)		< 0.01
Asia	46	1.48 (1.37–1.59)		< 0.01	41	1.35 (1.23–1.48)		< 0.01	105	1.64 (1.52–1.77)		< 0.01
South America	6	1.58 (1.07–2.32)		< 0.01	7	1.48 (1.15–1.91)		0.07	11	1.38 (1.09–1.75)		< 0.01
Oceania	3	1.42 (1.24 -1.63)		0.99	2	1.56 (0.80–3.04)		0.01	2	1.47 (0.90–1.75)		< 0.01
Africa	1	6.30 (1.25–31.62)		-	0	-		-	1	3.40 (1.01–11.48)		-
Income group[e]												
High income	74	1.58 (1.49–1.68)	0.02	< 0.01	66	1.28 (1.21–1.35)	0.09	< 0.01	96	1.49 (1.40–1.57)	0.12	< 0.01
Middle or low income	17	1.32 (1.14–1.52)		< 0.01	13	1.50 (1.26–1.78)		0.05	64	1.65 (1.47–1.87)		< 0.01
Year of publication												

Table 1 (continued)

Strata	Current smokers				Former smokers				Ever smokers			
	N. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N*. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#	*N*. studies	Pooled RR (95% CI)	*p*-value*	*p*-value#
≤ 2002	35	1.56 (1.38–1.76)	0.68	< 0.01	32	1.30 (1.19–1.42)	0.09	0.02	56	1.50 (1.39–1.63)	0.44	< 0.01
2003–2013	26	1.53 (1.37–1.71)		< 0.01	21	1.44 (1.28–1.61)		< 0.01	51	1.63 (1.46–1.83)		< 0.01
≥ 2014	31	1.47 (1.38–1.58)		< 0.01	29	1.23 (1.14–1.34)		< 0.01	57	1.50 (1.37–1.65)		< 0.01

NOS Newcastle Ottawa Scale

*p-value for heterogeneity across strata

#p-value for heterogeneity within strata

[a]Type of controls for case–control studies only. Studies considering both studies with hospital and with population controls were not included

[b]Endpoint for cohort studies only. Studies providing RRs for both incidence and mortality were considered in both categories

[c]Studies in which the number of cases was not reported were excluded

[d]Studies conducted in multiple countries from different geographic areas were not included

[e]Studies conducted in multiple countries with different income groups were not included

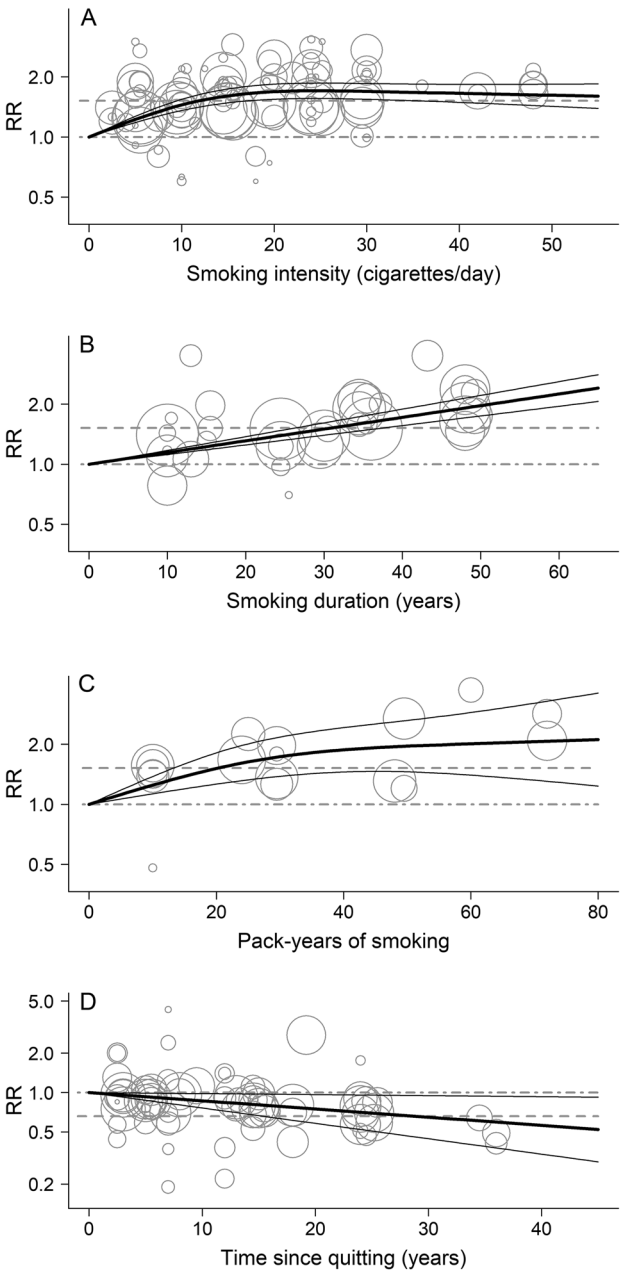

Fig. 3 Relative risk (RR) for the dose–response relationships between cigarette smoking intensity, duration, pack-years, and time since quitting and gastric cancer. **A** cigarette smoking intensity (based on 29 studies); **B** cigarette smoking duration (based on 9 studies); **C** pack-years of smoking (based on 5 studies); **D** time since quitting (based on 17 studies) ——— Linear model (**B** and **D**), or restricted cubic spline from a random-effects dose-response model (**A** and **C**); —— — 95% confidence interval of the linear model (**B** and **D**) or spline model (**A** and **C**); – . – . – RR for the reference category (never smokers in **A**, **B**, and **C**, current smokers in **D**); – – – – RR for current vs. never cigarette smokers (**A**, **B**, and **C**) or former vs. current cigarette smokers (**D**); unfilled circle RR for various exposure categories in each study included in the analysis. The area of the circle is proportional to the precision (i.e. to the inverse variance) of the RR

conducted in Oceania, and 3.40 in one study conducted in Africa; $p = 0.04$). Stratified analyses based on NOS quality assessment, categorizing studies into high (NOS ≥ 7) and low (NOS < 7) quality groups, indicated no significant differences in the RRs of GC for current, former, or ever smokers compared to never smokers.

Among studies with adjusted RR, a higher RR of GC for ever compared to never smokers was observed among studies conducted in Asia compared to non-Asian countries (RRs were 1.57 in studies conducted in Asia and 1.41 in studies conducted in other continents; $p = 0.05$; Supplementary Table 7). Further focusing on studies adjusting for *H. pylori*, this pattern persisted, revealing a higher RR in studies conducted in Asia compared to non-Asian countries (RRs were 1.57 in studies conducted in Asia and 1.41 in studies conducted in other continents; p-value < 0.01). Additionally, among studies adjusting for *H. pylori*, significantly higher RRs of GC for ever compared to never smokers were observed in middle- or low-income countries (RRs were 2.23 for middle/low- and 1.58 for high-income countries; $p = 0.04$) and among studies published before 2014 (RRs were 2.48 for studies published before 2014 and 1.42 for studies published after 2013; $p < 0.01$).

Publication bias

Evidence of possible publication bias emerged for current, former, and ever smokers either from the visual inspection of the funnel plots (Supplementary Fig. 9) or from the Egger's test ($p < 0.01$, $p = 0.03$, and $p = 0.02$, respectively).

Dose–response analysis

Figure 3 shows the dose–response relationships between smoking intensity (panel A), duration (panel B), pack-years (panel C), and time since quitting (panel D) and the risk of GC. We observed a nonlinear increase in GC risk with smoking intensity among current smokers. RRs of GC risk sharply increased already with a low number of cigarettes (five or ten) up to 20 cigarettes/day, the relation then levelling off for a higher amount of cigarettes/day. The RRs were 1.22 (95% CI 1.18–1.27) for five, 1.45 (95% CI 1.36–1.54) for ten, and 1.69 (95% CI 1.55–1.84) for 20 cigarettes/day (estimated using the curve functions reported in Supplementary Box 2). The RR of GC significantly increased linearly with increasing duration of smoking: RRs were 1.31 (95% CI 1.25–1.37) for 20 and 1.72 (95% CI 1.56–1.89) for 40 years of smoking. The analysis on pack-years of smoking revealed a nonlinear increase in GC risk among current smokers. For individuals with 20 pack-years of smoking, the RR was 1.38 (95% CI 1.26–1.81). This risk further escalated to a RR of 2.01 (95% CI 1.40–2.89) for individuals with 60 pack-years of smoking. The risk of GC significantly decreased linearly with increasing time since quitting, the RR for former compared with current smokers being 0.87 (95% CI 0.76–0.98) after 10 years since quitting, 0.75 (95% CI 0.58–0.96) after 20 years since quitting, and reaching the level of never smokers after 30 years since smoking cessation (RR: 0.65; 95% CI 0.44–0.95).

Discussion

The present systematic review and meta-analysis, conducted using an innovative methodology to identify original articles based on a combination of umbrella and traditional reviews [13, 15], is the most up-to-date, exhaustive, and comprehensive assessment of the association between cigarette smoking and the risk of gastric cancer. Pooled risk estimates from 205 original studies included in the meta-analysis showed a 53% and 30% increased GC risk in current and former smokers, respectively. The magnitude of the risk was similar across study designs for current and former smokers, but it was slightly higher in case–control studies for ever smokers. A sex difference emerged [11], male ever smokers having an approximatively 20% higher GC risk than female smokers.

The harmful effect of smoking affected any topographical subsite of GC, but the magnitude of the association was stronger for gastric cardia than for non-cardia cancers. Current smokers had a more than two-fold increased risk of gastric cardia cancer and a more modest 50% increased risk of distal GC. This updated risk quantification benefited from the inclusion of recently published studies that also allowed to quantify among former smokers an 80% increased risk of gastric cardia cancer and a 30% increased risk of distal GC. This differential excess risk of smoking has been hypothesized as one of the key factors to explain the diverging trends of cardia and non-cardia GCs over the last decades. While the falling rates of non-cardia GC were mainly due to the worldwide eradication of *H. pylori* infection [7], the increase in the incidence of cardia cancer over more recent calendar years [3, 7] could be consistent with the rise of smoking prevalence until the 1980s [63]. Furthermore, the increasing prevalence of obesity represents another potential influential factor that should be taken into account when considering trends in cardia gastric cancer.

The dose–response analysis carried out with flexible modelling techniques showed a non-linear association for smoking intensity, with a sharp risk increase up to 20 cigarettes per day, and a levelling thereafter. The risk linearly increased with smoking duration. An inverse linear dose–response association between time since stopping smoking and GC risk emerged; the risk of a former smoker reached the risk of a never smoker after 30 years since quitting smoking. This result has great relevance from a public health perspective and should encourage people to stop smoking to reduce

their risk. Our findings were generally consistent with those emerging from the meta-analyses published in the previous decades [12, 25, 26, 32], which were however based on a smaller number of studies.

GC is a multifactorial disease with a multistep etiology, resulting from a combination of environmental factors and genetic alterations. The main recognized risk factor is *H. pylori* infection, a class I human carcinogen [64]. We evaluated the role of *H. pylori* infection on the association between cigarette smoking and GC risk through a stratified analysis according to adjustment or matching for *H. pylori* infection. For ever smokers, we quantified an 81% increased risk of GC in 25 studies adjusting for *H. pylori* infection, and a more modest 50% increased risk in 139 studies who did not adjust for *H. pylori* infection.

This result supported an independent effect of smoking on GC risk, in line with the findings of a recent pooled-analysis of case–control studies [46].

People belonging to low socioeconomic classes have a higher smoking prevalence [65] and *H. pylori* infection rates [66], and also a higher risk of GC [67]. We, therefore, assessed a potential differential effect of smoking on GC risk in studies conducted in low/middle vs. high income countries. Noteworthy, our results showed similar risk estimates for former and ever smokers among strata of income; the pooled RR for current smokers emerging in 74 studies from high income countries was 1.58 as compared to 1.32 in 17 studies from low/middle income countries. However, most of the studies included in the meta-analysis were from Asian high-income countries, where GC incidence rates in 2017 were nearly 30/100,000 people [7]. Significant heterogeneity in risk estimates across study geographic area emerged; the highest risk for current smokers was found in studies conducted in North America (RR: 1.79), while studies from European countries showed more modest relative excess risks.

When we further stratified studies adjusting for *H. pylori* infection for geographic and temporal factors, we observed a higher increased risk of GC for ever smoking in Asian and low-/middle-income countries and in studies conducted before 2014. These findings underscore the need for nuanced consideration of geographic and temporal factors when interpreting the association between smoking and gastric cancer.

Several explanations of the mechanisms linking tobacco smoking to an increased risk of GC have been postulated. Gastric carcinogenesis is preceded by several precursor stages leading a transformation from a normal gastric mucosa to chronic gastritis, intestinal metaplasia and dysplasia. In vitro, cigarette smoke condensate exhibited a carcinogenic effect on the gastric mucosa [68]. In the early 1990's, Kneller and colleagues [69] showed that cigarette smoking nearly doubled the risk of transition from a normal gastric mucosa to dysplasia. Further evidence came from a study by You et al. [70] showing that smoking duration for more than 25 years was significantly associated to an increased risk for the progression of precursor lesions to dysplasia and GC. Tobacco products contain over 70 human carcinogens, including polycyclic aromatic hydrocarbons (PAH), nitrosamines and other *N*-nitroso compounds [4]. These carcinogens are be able to covalently bind to DNA, altering normal DNA functions and eventually leading to GC formation [71]. Several studies have investigated the interaction between some genes involved in the metabolic pathway of activation and detoxification of PAH, and tobacco smoking in gastric cancerogenesis. Polymorphisms in genes CYP1A1 (one of the main cytochrome P450 enzymes), CYP1A2, EPHX1, SULT1A1, NAT2 and GSTT1 modulated individual's susceptibility to GC risk in combination with the effect of smoking [72, 73].

The limitations of this work were those typical of meta-analyses of epidemiological studies. Case–control and cohort studies are prone to selection and recall bias. A differential misclassification of exposure may have occurred since information on smoking intensity and duration was self-reported in most studies. We reasonably retained that the impact of these biases was limited; in fact, for both current and former smokers, risk estimates were not significantly heterogeneous across study types. It has also been suggested that smokers may be over-represented among hospital-based controls, biasing the association towards the null. Our results did not support this hypothesis, showing on the contrary stronger associations among hospital-based as compared with population-based case–control studies, in line with the findings of a recent pooled-analysis of case–control studies [46].

A consistent heterogeneity between studies was found for each smoking status. This may be the results of pooling data from studies conducted with different methodologies, considering different definitions of smoking, and including subjects with various characteristics and background risk levels. We allowed for heterogeneity between studies using random-effects models, although these models gave more conservative estimates but not resolved heterogeneity. We investigated possible putative sources of heterogeneity in risk estimates through stratified analyses according to cancer topographical subsite, socioeconomic status, adjustment for *H. pylori* infection and study characteristics. However, these variables did not contribute so much to explain the observed heterogeneity. Among the considered strata, we did not have the possibility to estimate the association in *H. pylori* positive and *H. pylori* negative subjects to assess any multiplicative effect of smoking. The results of a recent published Finnish cohort study showed that gastric noncardia cancers remains elevated even after *H. pylori* eradication [74], enforcing the role of smoking as an independent risk

factor for GC. Finally, we did not considered stratification by GC histotype (e.g., diffuse, intestinal) [75, 76].

A comprehensive quality assessment of the included studies was performed using the NOS [77], revealing no significant differences of GC cancer for current, former, and ever smokers according to the quality of the studies measured with the NOS. While the NOS provides a structured framework for evaluating study quality based on certain parameters, we acknowledge some inherent limitations and subjectivity in its scoring system. We, therefore, preferred to consider also stratified analyses based on objective study quality parameters, such as adjustments for any confounding factor, adjustment or matching for *H. pylori* infection, and study population size (determined by the number of GC cases). Considering these three measures, the high-quality studies (those providing adjusted estimates and those with larger size) showed lower but still statistically significant excess GC risks in ever smokers compared with never smokers.

Our systematic review and meta-analysis has several strengths. The innovative methodology used to identify original articles based on a combination of umbrella and traditional reviews [13, 15] allowed to include over 200 epidemiological studies investigating the association between cigarette smoking and GC risk, making this meta-analysis the most comprehensive one on the issue. We were also able to identify publications from the IARC monographs [4, 49] or from other sources that were not captured in previous meta-analyses [25, 26, 32], although satisfying their inclusion criteria. The screening process of all the retrieved publications was carefully carried out to avoid data overlapping arising when original studies have been subsequently included in pooled-analyses and/or consortia of individual participating data meta-analyses. In addition, we modelled the risk functions best describing the dose–response relationships with smoking intensity, duration and time since stopping smoking using a flexible meta-analytic random-effects model based on restricted cubic splines [57].

In conclusion, this comprehensive and up-to-date meta-analysis confirmed that tobacco smoking is an independent risk factor for gastric cancer. In particular, the risk of cardia GC is two-fold for current compared with never smokers. We showed a non-linear association between smoking intensity and gastric cancer risk with a sharply increased risk up to 20 cigarettes per day. The risk linearly increased with the duration of smoking, without any levelling. People should avoid smoking, and current smokers should quit to reduce the risk.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-023-01459-1.

Acknowledgements We thank Elisa Borroni, Giulia Peveri, and Xiaoqiu Liu for their contributions in the literature screening process. The research leading to these results has received funding from AIRC under MFAG 2021—ID. 25840 project—P.I. Lugo Alessandra. The work of SG was partially supported by the Italian League Against Cancer (LILT), Milan, Italy.

Author contributions S.G. and A.L. had the original idea of the work and designed the innovative methodology for the identification of original publications. I.P., C. Santucci and V.V. identified the articles, screened them for eligibility, and extracted the data, with the help of S.G. and A.L. A.L., I.P. and V.V. performed the statistical analyses. S.G., A.L., I.P. and M.R. drafted the manuscript. V.B., C.B., G.C., C. Santucci, and C. Specchia provided statistical and epidemiological supervision. All authors contributed to critical review, editing, and revision of the manuscript draft, and approval of the final version.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

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