Dose-risk relationships between cigarette smoking and cervical cancer: a systematic review and meta-analysis

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Objective **Cervical cancer (CC) is the fourth most frequent cancer worldwide. Cigarette smoking has been shown to influence CC risk in conjunction with human papillomavirus (HPV) infection. The aim of this study is to provide the most accurate and updated estimate of this association and its dose-response relationship.**

Methods **Using an innovative approach for the identification of original publications, we conducted a systematic review and meta-analysis of studies published up to January 2021. Random effects models were used to provide pooled relative risks (RRs) of CC for smoking status. Dose-response relationships were evaluated using one-stage random effects models with linear or restricted cubic splines models.**

Results **We included 109 studies providing a pooled RR of invasive CC and preinvasive lesions, respectively, of 1.70 [95% confidence interval (CI), 1.53–1.88] and 2.11 (95% CI, 1.85–2.39) for current versus never smokers, and, respectively, 1.13 (95% CI, 1.02–1.24) and 1.29 (95% CI, 1.15–1.46) for former versus never smokers. Considering HPV does not alter the positive association or its magnitude. Risks of CC sharply increased with few cigarettes (for 10 cigarettes/day, RR = 1.72; 95% CI, 1.34–2.20 for invasive CC and RR = 2.13; 95% CI, 1.86–2.44 for precancerous lesions). The risk of CC increased with pack-years and smoking duration and decreased linearly with time since quitting, reaching that of never smokers about 15 years after quitting.**

Conclusion **This comprehensive review and meta-analysis confirmed the association of smoking with CC, independently from HPV infection. Such association rose sharply with smoking intensity and decreased after smoking cessation.** ***European Journal of Cancer Prevention*** **XXX: 000–000**

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Introduction

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of death from cancer among women worldwide, with about 604 000 new cases and 342 000 deaths in 2020 (Sung *et al.*, 2021).

Both the incidence and mortality of CC vary widely according to geographic area, with the majority of cases occurring in less developed regions. The highest rates were found in sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean (Vaccarella *et al.*, 2017).

The two major histological types of invasive CC, adenocarcinoma and squamous-cell carcinoma, as well as the preinvasive lesions, that is cervical intraepithelial neoplasia (CIN) of grade 1, 2 or 3 or carcinoma *in situ* (CIS), share many risk factors (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). The strongest factor associated with CC is human papillomavirus (HPV) infection. Persistent infection with certain high-risk types of genital HPV is a major factor in the development of CIN and invasive CC (Walboomers *et al.*, 1999; Koshiol *et al.*, 2008). To date, approximately 15 oncogenic HPV types have been identified, of which HPV-16 and HPV-18 are the most prevalent in CC, accounting for approximately 70% of cases worldwide (IARC, 1995, 2007, 2012a; de Sanjose *et al.*, 2010).

Since 2009, the WHO has recommended the inclusion of HPV vaccination of girls aged 9–14 years into national immunization programmes (WHO, 2009). However, since HPV vaccines do not protect against all high-risk HPV types, vaccination should be part of a comprehensive approach to CC prevention and control that includes secondary prevention through screening for abnormal cervical cells and precancerous lesions (WHO, 2020) preferably using HPV DNA-based testing to detect precancerous lesions (Accetta *et al.*, 2010; WHO, 2021).

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Infection from HPV has been established as a necessary, but not solely sufficient, cause of CC (Walboomers *et al*., 1999). Additional risk factors have been identified to influence CC risk in conjunction with HPV infection (Castellsague and Munoz, 2003; Zhang *et al*., 2020). Besides parity, use of oral contraceptives, immunosuppression, infections with other sexually transmitted diseases and poor nutrition, also tobacco smoking has been associated with the development of CC.

A positive association between smoking and incidence of cervical squamous-cell carcinoma, which accounts for approximately 90% of all CC (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007), and CIN has been shown consistently over several decades. The hypothesis of an increased risk of CC among smokers was first suggested by Winkelstein in 1977 (Winkelstein, 1977), subsequently confirmed in the review conducted in 1986 by the International Agency for Research on Cancer (IARC), even if the association was confounded by sexual behavior variables, since, at that time, the causality of HPV in CC was not yet identified (1986). In 2003, a pooled analysis assessed the role of smoking as a cofactor of HPV in the cause of squamous-cell cervical carcinoma and CIS showing a more than double-fold risk of CC for smoking compared with nonsmoking HPV-positive women (Plummer *et al*., 2003). In 2004, the IARC established a causal association of cervical squamous-cell carcinoma with smoking (IARC, 2004), whereas, in the small number of studies available for adeno- and adenosquamous-cell carcinoma, no consistent association was observed (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006). Dose-response associations with smoking intensity were also reported in many of the studies where such associations were examined, whereas no clear trends with duration and time since stopping smoking were observed (Plummer *et al*., 2003; International Collaboration of Epidemiological Studies of Cervical Cancer, 2006).

To our knowledge, in the literature, there are no accurate and recently published meta-analyses on the relationship between smoking and CC neither meta-analytic estimates of the dose-response relationships. In order to provide an accurate and up-to-date quantification of the association between cigarette smoking and CC risk, we conducted the present meta-analysis by taking into account all the smoking-related variables and the histologic and severity-related CC variables as well as the HPV infection. We also showed the functions that best describe the dose-response relationships between smoking intensity, duration, pack-years and time since quitting and risks of invasive CC or preinvasive lesions, and provided meta-analytical estimates of such dose-response functions.

Materials and methods

The present systematic review and meta-analysis on CC were conducted following the methodology described in detail in a previous publication, which combines umbrella and traditional reviews (Lugo *et al*., 2017). This meta-analysis on CC risk was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Box 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*; Page *et al*., 2021) and is part of a series of systematic reviews and meta-analyses on the association between cigarette smoking and the risk of cancer at any site (Lugo *et al*., 2018; Liu *et al*., 2019; Santucci *et al*., 2019; Botteri *et al*., 2020; Lugo *et al*., 2020). The study protocol has been registered on PROSPERO (registration number CRD42017063991).

Search strategy

As a first step, through a full literature search on various databases (PubMed/MEDLINE, Embase, Institute for Scientific Information Web of Science and the Cochrane Database of Systematic Reviews), we conducted an umbrella review to identify all meta-analyses, pooled analyses and reviews on the association between cigarette smoking and the risk of cancer at any site, published up to 14 January 2020 (Lugo *et al*., 2017). The search string included combinations of medical subject headings (MeSH) and text words related to cancer (not limited to CC) and tobacco or smoking (Lugo *et al*., 2017).

Among 220 eligible articles, we identified nine systematic reviews/meta-analyses (Licciardone *et al*., 1990; Sood, 1991; Castellsague and Munoz, 2003; Haverkos *et al*., 2003; Berrington de Gonzalez *et al*., 2004; Gandini *et al*., 2008; Nakamura *et al*., 2009; Gadducci *et al*., 2011; Sugawara *et al*., 2019) and seven pooled analyses (Moreno *et al*., 2002; Munoz *et al*., 2002; Plummer *et al*., 2003; International Collaboration of Epidemiological Studies of Cervical Cancer, 2006; Katanoda *et al*., 2008; Louie *et al*., 2011; Zheng *et al*., 2014) reporting data on the association between smoking and the risk of CC (Supplementary Fig. 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). We also considered the two IARC monographs on tobacco smoking (IARC, 2004, 2012b) and two Surgeon General's Reports (US Department of Health and Human Services, 2001, 2004). These 20 reports identified 140 nonduplicate original study publications providing information on the relation between tobacco smoking and CC risk.

In a second step, we carried out an update of the scientific literature on PubMed/MEDLINE and Embase to identify all the original studies published between 1 January 2008 [i.e. the year of the conduction of the last comprehensive review on the issue (IARC, 2012b)] and 1 January 2021. The search string was comprehensive and included combinations of MeSH and text words related to CC and tobacco or smoking (Supplementary Box 2, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). The nonduplicate original publications

and pooled analyses found in the updated search were 1969; after the exclusion by title/abstract screening of ineligible articles and the inclusion of 13 additional publications from other sources, the updated literature search resulted in 74 original study publications and pooled analyses (Supplementary Fig. 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). Eligibility was independently assessed by two reviewers (G.C. and A. Lachi). Merging the nonduplicate publications identified through the umbrella review and those identified in the update, we obtained 214 nonduplicate original publications that were screened on the basis of their full text considering the eligibility criteria.

Eligibility criteria

We included in the present meta-analysis all studies that satisfied the following eligibility criteria: (a) they were case–control studies (including nested case–control studies or pooled analyses of case–control studies) or cohort studies (including pooled analyses of cohort studies); cross-sectional studies were excluded from the review, since they report exposure and outcome at the same point in time; (b) they were published as original articles in English; (c) they provided data on humans in the general female population, thus excluding publications based on patients with cancer; (d) they provided information on cigarette smoking; (e) they reported risk estimates, including risk ratios, odds ratios, hazard ratios or mortality rate ratios – all referred to as relative risk (RR) – of CC (adenocarcinoma, squamous-cell carcinoma, adenosquamous-cell carcinoma and also for CIN 1, 2, 3 and CIS) for at least one variable among smoking status (current, former or ever smoking) and dose-response variables (intensity, duration, pack-years and time since quitting), compared with never or current cigarette smokers, and reported the corresponding 95% confidence intervals (CIs) or provided sufficient information to compute them.

We considered as eligible only articles providing RRs specifically for CC (International Classification of Diseases, ICD 10: C53.9), CIN3 or CIS (ICD 10: D06) and CIN 1 or 2 (ICD 10: N87).

Out of the 214 total original publications, 82 were excluded because they did not meet these eligibility criteria (Supplementary Fig. 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). Reasons for exclusion are reported in Supplementary Table 1 (Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). When the results of the same study appeared in more than one original publication, we considered data published in the most recent or complete article.

Data extraction

For each eligible study, we collected information on the CC type under study (e.g. if histologically confirmed and the histological type for invasive cancers or the severity for dysplasia).

We then 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, outcome and sample size), model used to compute the estimates (including the list of adjustments), and, for various exposure categories, the RR estimates (with the corresponding 95% CIs) and, when available, the number of cases and controls (or subjects at risk/person-years for cohort studies). When necessary, we used the method described by Hamling *et al.* (2008) for pooling nonindependent estimates to change the reference category or to collapse the RRs for two or more categories when the reference group was the same.

Statistical methods

We derived pooled estimates of the RRs of invasive CC (both adenocarcinoma and squamous-cell carcinoma) and preinvasive lesions (CIN1, CIN2, CIN3 and CIS) for current, former and ever smokers compared with never smokers using random effects meta-analytic models in order to take into account the heterogeneity of risk estimates (DerSimonian and Laird, 1986). 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 (Higgins and Thompson, 2002). Meta-analyses were carried out for the overall sample and separately for case–control and cohort studies, as well as stratified according to different study and population characteristics, including geographic area, type of controls (for case–control studies), endpoint (for cohort studies), year of publication, type of cancer, HPV infection, and whether or not estimates were provided adjusting for number of sexual partners or HPV infection, as indicated by either the presence of HPV DNA in cervical cells or of anti-HPV serum antibodies.

To evaluate the publication bias, we examined the funnel plots (Peters *et al.*, 2008) and applied the Egger's test for funnel plot asymmetry (Egger *et al.*, 1997). We investigated both linear and nonlinear relationships between smoking intensity, pack-years, duration (for current vs. never smokers) and time since quitting (for former vs. current smokers), and the log RR of invasive CC or precancerous lesions. For each exposure variable, we tested the log-linearity using the Wald test. The nonlinear relationships were evaluated using one-stage random effects dose-response models; these methods were recently found to be the most suited for dose-response meta-analyses (Crippa *et al.*, 2019). In case of nonlinearity, we used restricted cubic splines with three knots at fixed percentiles (10, 50 and 90%) of various distributions (Desquilbet and Mariotti, 2010). For each exposure category, the level of exposure was assigned as the midpoint between the upper and the lower bounds of the category. For open-ended upper categories, the level of exposure was determined as 1.2 times the lower bound (Berlin *et al.*, 1993;

Bagnardi *et al*., 2015). In a few studies where covariance among log RR was not computable, we proportioned the distribution of cases or controls in various dose-response exposure categories on the basis of data from all the other studies combined (Crippa and Orsini, 2016). All statistical analyses were performed using the R software, version 4.1.0 (R Development Core Team, 2021), in particular the 'meta' and 'dosresmeta' packages (Crippa and Orsini, 2016).

Results

Characteristics of the included studies

Out of the 132 eligible articles, 23 were excluded because their data were included in other publications (Supplementary Table 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*). Thus, 109 articles were included in the present meta-analysis. Supplementary Table 2 and Supplementary Table 3, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*, summarize main characteristics of the included case–control (N = 83) and cohort (N = 26) studies, respectively. Supplementary Table 4 Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*, shows the list of publications whose data have been partially excluded from the meta-analysis.

Original articles included in meta-analysis were published between 1973 and 2020 and were based on a total of 47 552 CC cases (40 409 from case–control and 7143 from cohort studies). Thirty-one studies on invasive CC provided a measure of association – or information to derive it – for current smokers, 23 for former smokers, and 45 for ever smokers, compared with never smokers. Moreover, 41 studies reported RR estimates for smoking intensity (27 among current smokers), 25 for smoking duration (eight among current smokers), 18 for pack-years (eight among current smokers), and five for time since quitting smoking. Among studies on precancerous lesions, 39 studies provided a measure of association for current smokers, 25 for former smokers, and 42 for ever smokers, compared with never smokers.

Invasive cervical cancer

The pooled RR of invasive CC for current versus never smokers was 1.70 (95% CI, 1.53–1.88) overall, with no significant differences by study design (Fig. 1). For all pooled estimates, there was significant between-studies heterogeneity. The summary RR for invasive CC for former versus never cigarette smokers was 1.13 (95% CI, 1.02–1.24) with no significant differences by study design (Fig. 2). The corresponding figure for ever smokers was 1.59 (95% CI, 1.43–1.76) (Supplementary Fig. 2, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*).

Significant differences in the risk of invasive CC were observed for current smokers according to geographic area with higher RR in South America and Oceania compared with other countries (P for heterogeneity across strata $P < 0.01$, Table 1) and for ever smokers according to year of publication (RR were 1.43, 1.31 and 1.87 for studies published respectively before 1995, in 1996–2006 and after 2007, $P < 0.01$) and to adjustment for number of sexual partners ($P < 0.01$). The pooled RR of squamous-cell carcinoma for current versus never smokers was 1.59 (95% CI, 1.40–1.80), whereas for adenocarcinoma or adenosquamous carcinoma a nonsignificant association with current smoking was observed (RR = 1.06; 95% CI, 0.14–7.96) (Table 1).

No significant differences by study design, type of control, endpoint, type of cancer, HPV infection and HPV adjustment were recorded (Table 1).

Possible publication bias emerged from studies of invasive CC on current (Supplementary Fig. 3, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*), former (Supplementary Fig. 4, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*) and ever (Supplementary Fig. 5, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*) smokers either on visual inspection of the funnel plots or by Egger's test ($P < 0.01$, $P = 0.045$, and $P < 0.01$, respectively).

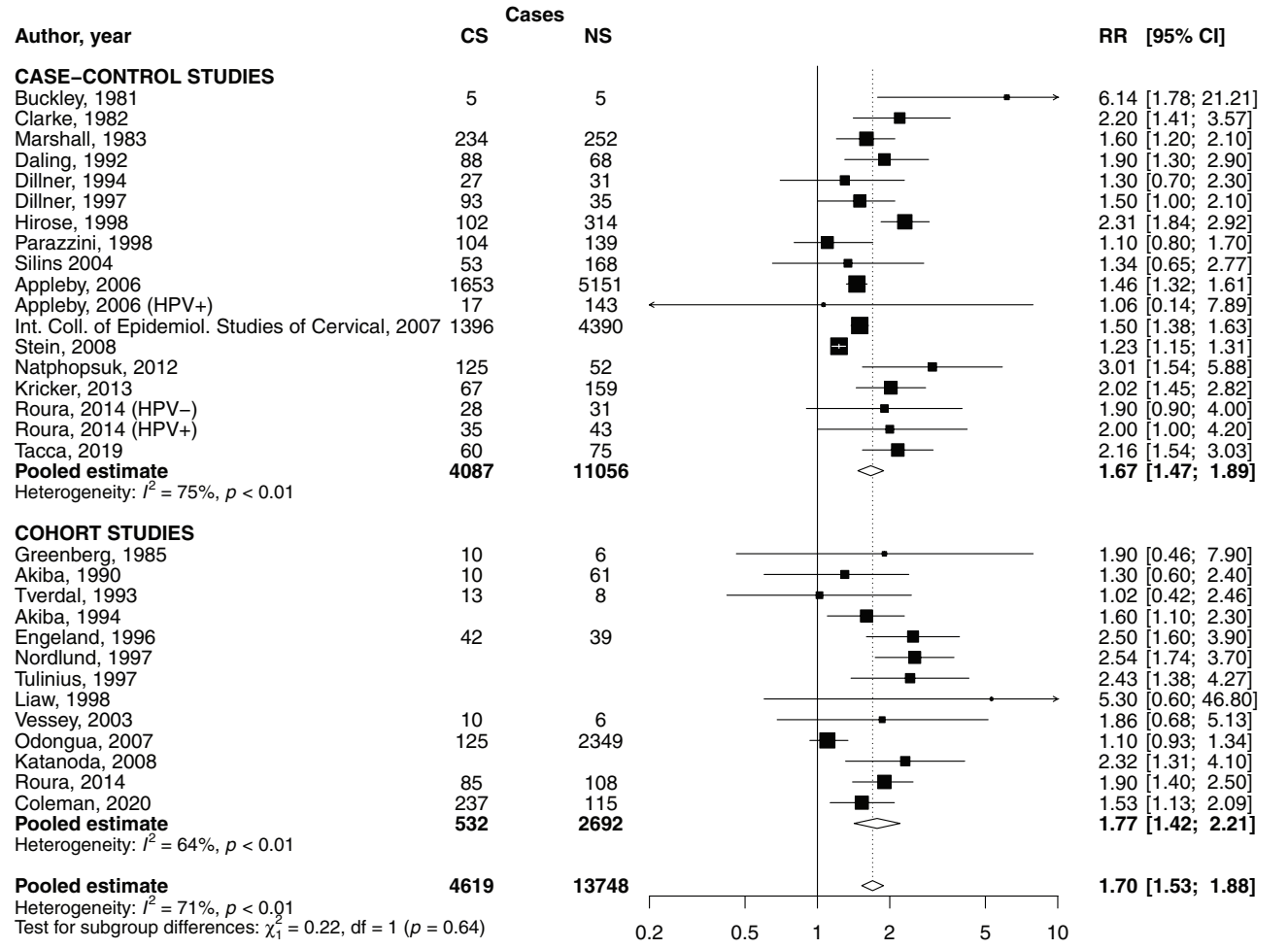
Preinvasive lesions

The pooled RR of preinvasive lesions (CIN 1, 2, 3, CIS or unspecified) for current, former and ever versus never smokers were respectively 2.11 (95% CI, 1.85–2.39), 1.29 (95% CI, 1.15–1.46) and 1.77 (95% CI, 1.58–1.99) with no significant differences by study design (Table 2). For all pooled estimates, except for former smokers, there was significant between-studies heterogeneity.

Significant differences in the risk of preinvasive lesions were observed for current and ever versus never smokers according to geographic area (P for heterogeneity across strata $P < 0.01$ and $P = 0.03$, respectively, Table 2). Significant differences in the risk of preinvasive lesions were observed also for current smokers according to year of publication (RR were 2.55, 1.55 and 1.90 for studies published, respectively, before 1995, in 1996–2006 and after 2007, $P = 0.01$) and according to HPV adjustment (RR were 2.28 for studies that adjusted and 1.59 for those that did not adjust for HPV, $P = 0.03$).

No significant differences were recorded by study design, type of control, type of lesion, HPV infection and adjustment for number of sexual partners. As for invasive CC, possible publication bias emerged from studies on current, former and ever smokers (data not shown). In Supplementary Table 5, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*, RRs of developing CIN2+ (CIN2, CIN3 and invasive CC) for current, former and ever cigarette smokers are shown.

Fig. 1



Forest plot for study-specific and summary relative risk (RR) of invasive cervical cancer for current cigarette smokers (CS) versus never smokers (NS), overall and by study design. CI, confidence interval; HPV+, human papillomavirus positive; HPV–, human papillomavirus negative.

Dose-response relationships

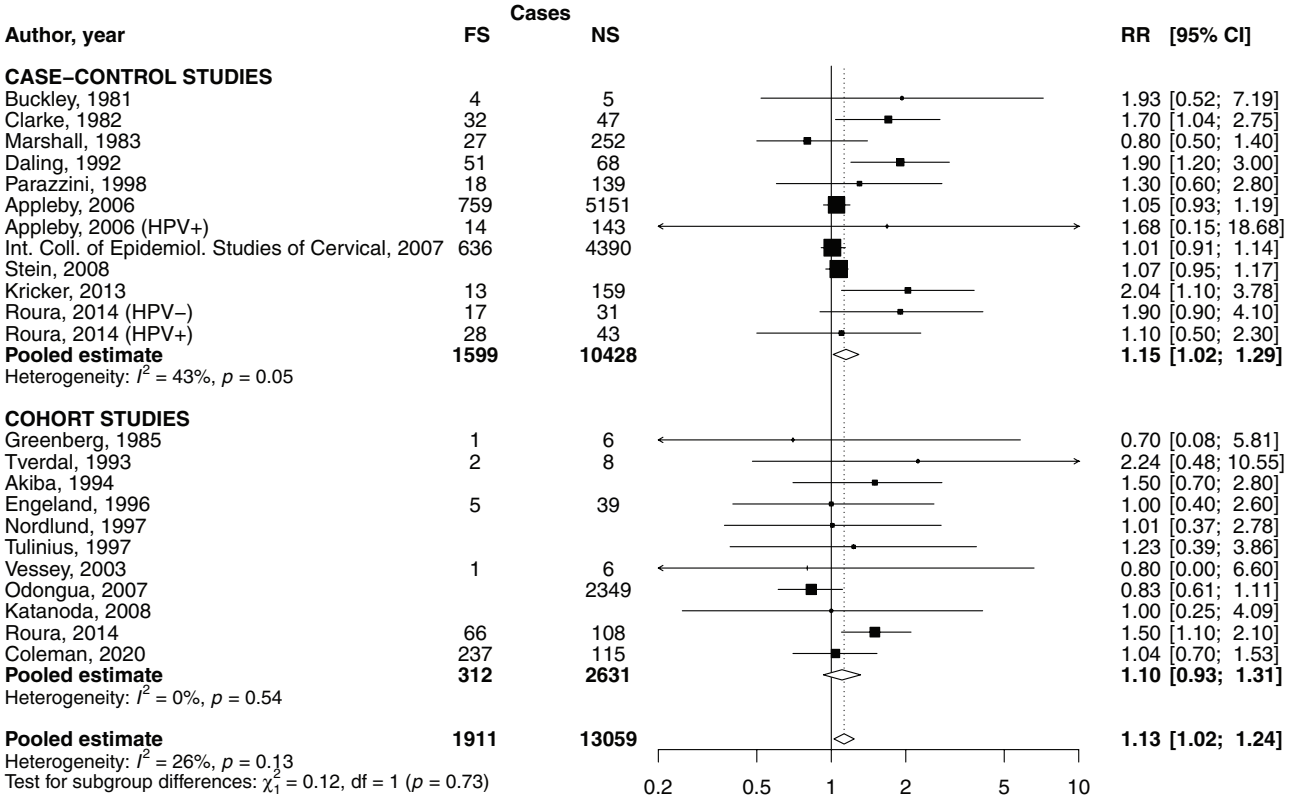
Figure 3 shows the dose-response relationships between smoking intensity (panel a), duration (panel b), pack-years (panel c), and time since quitting (panel d) and the risk of invasive CC. The risk rose nonlinearly with smoking intensity up to 20 cigarettes/day and declined slightly thereafter. The RRs for current versus never smoker were 1.72 (95% CI, 1.34–2.20) for 10 cigarettes/day, 1.91 (95% CI, 1.46–2.49) for 20 cigarettes/day and 1.86 (95% CI, 1.14–3.03) for 30 cigarettes/day (Fig. 3a). Risk rose linearly with smoking duration (beta = 0.0088; P = 0.43) and number of pack-years (beta = 0.0458; P = 0.06; Fig. 3b and c). RRs for current versus never smokers were 1.09 (95% CI, 0.88–1.36) for 10 years of smoking, 1.19 (95% CI, 0.77–1.85) for 20 years and 1.30 (95% CI, 0.67–2.51) for 30 years. The RRs were 1.26 (95% CI, 0.99–1.60) for 5 pack-years, 1.58 (95% CI, 0.98–2.56) for 10 pack-years, and 2.50 (95% CI, 0.96–6.53) for 20 pack-years, even though RRs by pack-year were based on just one study.

There was an inverse, significant linear relationship between time since quitting and the risk of invasive CC (Fig. 3d). RRs for former versus current smokers were 0.72 (95% CI, 0.66–0.80) for 10 years since quitting and 0.53 (95% CI, 0.43–0.64) for 20 years since quitting. The RR for former versus current smokers reached the one for never versus current smokers (0.59; 95% CI, 0.50–0.69) after 16.5 years from quitting.

Figure 4 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 preinvasive lesions.

A nonlinear increase in precancerous lesions risk was observed with increasing smoking intensity: the RR for current versus never smokers was 2.13 (95% CI, 1.86–2.44) for 10 cigarettes/day, 2.71 (95% CI, 2.36–3.11) for 20 cigarettes/day and 2.88 (95% CI, 2.30–3.60) for 30 cigarettes/day (Fig. 4a). The same trend was observed by pack-year,

Fig. 2



Forest plot for study-specific and summary relative risk (RR) of invasive cervical cancer for former cigarette smokers (FS) versus never smokers (NS), overall and by study design. CI, confidence interval; HPV+, human papillomavirus positive; HPV–, human papillomavirus negative.

where the RRs were 1.74 (95% CI, 1.44–2.09) for 5 pack-years, 2.07 (95% CI, 1.63–2.63) for 10 pack-years and 2.15 (95% CI, 1.20–3.85) for 20 pack-years (Fig. 4c).

There was a nonlinear increase followed by a declining trend with smoking duration (Fig. 4b). The RRs were 3.19 (95% CI, 1.44–7.03) for 10 years of smoking, 2.14 (95% CI, 1.40–3.28) for 20 years and 1.37 (95% CI, 0.84–2.23) for 30 years.

Precancerous lesions risk linearly decreased with time since quitting cigarette smoking, with RRs for former versus current smokers being 0.62 (95% CI, 0.51–0.77) for 10 years of quitting and 0.39 (95% CI, 0.26–0.59) for 20 years of quitting. The RR for former versus current smokers reached the one for never versus current smokers (0.47; 95% CI, 0.33–0.65) after 16 years from quitting (Fig. 4d).

The estimated functions to model the dose-response curves are reported in Supplementary Box 3, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A367*.

Discussion

In this comprehensive review and meta-analysis conducted using an original design, we summarized the available evidence from 109 epidemiological studies – out of 132 eligible ones – confirming a significant association between cigarette smoking and the risk of CC, both for invasive cancer and preinvasive lesions. Current and former smokers showed, respectively, a 70 and 13% higher risk of invasive CC compared with never smokers, and a 111 and 29% higher risk of preinvasive lesions. Overall, we found an increased CIN2+ risk of 99% in current and 29% in former smokers compared with never smokers. The association between smoking and CC resulted independent from other CC risk factors, that is HPV infection.

The findings of the present study are consistent with those from previous meta-analyses (Licciardone *et al.*, 1990; Haverkos *et al.*, 2003; Berrington de Gonzalez *et al.*, 2004; Gandini *et al.*, 2008) or pooled analyses (International Collaboration of Epidemiological Studies of Cervical Cancer 2006, 2007; Zheng *et al.*, 2014; Feng *et al.*, 2017), although they were based on a smaller number of studies. Recently, a systematic review and meta-analysis on CC and current smoking were published, reporting an excess risk of CIN2+ for current or ever versus never smokers consistent with our estimate (OR = 2.03; 95%

Table 1 Pooled relative risks and corresponding 95% confidence intervals of invasive cervical cancer for current, former, and ever cigarette smokers versus never cigarette smokers, overall and in strata of selected characteristics

	Current smokers				Former smokers				Ever smokers			
Strata	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]
Total	31	1.70 (1.53–1.88)	-	<0.01	23	1.13 (1.02–1.24)	-	0.13	45	1.59 (1.43–1.76)	-	<0.01
Geographic area[c]												
North America	4	1.70 (1.43–2.02)	<0.01	0.55	4	1.28 (0.87–1.89)	0.07	0.04	4	1.60 (1.31–1.94)	0.11	0.25
Europe	14	1.80 (1.49–2.18)		0.07	11	1.41 (1.12–1.77)		0.98	16	1.51 (1.32–1.72)		0.20
Asia	7	1.83 (1.27–2.63)		<0.01	3	0.96 (0.67–1.37)		0.30	11	1.62 (1.26–2.08)		0.01
South America	1	2.16 (1.54–3.03)		-	0	-		-	1	2.27 (0.88–5.86)		-
Oceania	1	2.02 (1.45–2.82)		-	1	2.04 (1.10–3.78)		-	1	2.03 (1.49–2.76)		-
Africa	1	1.23 (1.15–1.31)		-	1	1.07 (0.96–1.19)		-	3	3.16 (1.05–9.50)		<0.01
Central America	3	1.48 (1.39–1.58)		0.87	2	1.05 (0.93–1.19)		0.70	5	1.28 (1.09–1.51)		0.12
Study design												
Case–control	18	1.67 (1.47–1.89)	0.64	<0.01	12	1.15 (1.02–1.29)	0.73	0.05	32	1.61 (1.42–1.82)	0.70	<0.01
Cohort	13	1.77 (1.42–2.21)		<0.01	11	1.10 (0.93–1.31)		0.54	13	1.54 (1.30–1.83)		0.06
Types of control[d]												
Hospital	9	1.79 (1.39–2.31)	0.97	<0.01	5	1.17 (0.88–1.55)	0.07	0.17	16	1.87 (1.38–2.52)	0.26	<0.01
Population	6	1.81 (1.44–2.27)		0.75	4	1.70 (1.28–2.25)		0.67	10	1.55 (1.39–1.73)		0.59
Endpoint[e]												
Incidence	7	1.87 (1.36–2.57)	0.60	<0.01	7	1.13 (0.86–1.48)	0.99	0.24	7	1.57 (1.22–2.03)	0.98	0.03
Mortality	7	1.69 (1.37–2.07)		0.53	5	1.13 (0.82–1.56)		0.89	7	1.57 (1.29–1.91)		0.41
Year of publication												
≤1995	9	1.68 (1.42–2.00)	0.71	0.38	7	1.44 (1.06–1.96)	0.18	0.25	16	1.43 (1.27–1.60)	<0.01	0.24
1996–2006	11	1.81 (1.46–2.25)		<0.01	7	1.06 (0.94–1.19)		1.00	12	1.31 (1.20–1.44)		0.42
≥2007	11	1.62 (1.40–1.89)		<0.01	9	1.10 (0.97–1.26)		0.07	17	1.87 (1.52–2.32)		<0.01
Type of cancer												
Adenocarcinoma	1	1.06 (0.14–7.96)	0.69	-	1	1.68 (0.15–18.75)	0.78	-	3	1.44 (0.89–2.34)	0.15	0.94
Squamous cervical cancer	5	1.59 (1.40–1.80)		0.08	4	1.18 (0.97–1.44)		0.01	7	2.21 (1.61–3.03)		<0.01
HPV												
Negative	1	1.90 (0.90–4.01)	0.97	-	1	1.90 (0.89–4.06)	0.34	-	3	1.82 (1.19–2.78)	0.86	0.78
Positive	2	1.86 (0.95–3.66)		0.56	2	1.14 (0.55–2.37)		0.74	4	1.91 (1.25–2.94)		0.36
HPV adjustment												
No	28	1.69 (1.52–1.89)	0.86	<0.01	23	1.13 (1.02–1.24)	-	0.16	43	1.60 (1.44–1.78)	0.47	<0.01
Yes	3	1.76 (1.13–2.75)		0.16	0	-		-	2	1.32 (0.81–2.17)		0.78
Life partners adjustment												
No	25	1.78 (1.53–2.06)	0.07	<0.01	18	1.17 (1.02–1.34)	0.59	0.26	35	1.72 (1.48–2.01)	<0.01	<0.01
Yes	6	1.50 (1.34–1.68)		0.13	5	1.10 (0.95–1.29)		0.12	10	1.30 (1.23–1.37)		0.56

CI, confidence interval; HPV, human papillomavirus; RR, relative risk.

[a]*P*-value for heterogeneity across strata.

[b]*P*-value for heterogeneity within strata.

[c]Studies in multiple countries from different areas were not included.

[d]Types of control only for case–control studies.

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

Table 2 Pooled relative risks and corresponding 95% confidence intervals of cervical intraepithelial lesions for current, former, and ever cigarette smokers versus never cigarette smokers, overall and in strata of selected characteristics

	Current smokers				Former smokers				Ever smokers			
Strata	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]	Studies (no.)	Pooled RR (95% CI)	*P*-value[a]	*P*-value[b]
Total	39	2.11 (1.85–2.39)	-	<0.01	25	1.29 (1.15–1.46)	-	0.09	42	1.77 (1.58–1.99)	-	<0.01
Geographic area[c]												
North America	15	2.13 (1.66–2.74)	<0.01	<0.01	9	1.33 (1.11–1.60)	0.17	0.66	11	1.73 (1.34–2.23)	0.03	<0.01
Europe	14	2.15 (1.93–2.40)		0.43	10	1.48 (1.14–1.92)		0.07	18	2.03 (1.74–2.37)		0.01
Asia	4	1.50 (0.77–2.91)		0.22	1	0.32 (0.08–1.27)		-	5	1.73 (1.04–2.87)		0.07
South America	2	5.47 (2.35–12.71)		0.52	1	1.51 (0.27–8.51)		-	2	1.73 (0.47–6.38)		0.05
Oceania	3	1.86 (1.36–2.54)		<0.01	3	1.17 (1.04–1.32)		0.45	3	1.60 (1.15–2.23)		<0.01
Africa	0	-		-	0	-		-	1	8.90 (1.63–48.75)		-
Central America	1	0.81 (0.57–1.16)		-	1	1.04 (0.72–1.51)		-	2	1.09 (0.77–1.54)		0.07
Study design												
Case–control	33	2.16 (1.86–2.51)	0.37	<0.01	20	1.28 (1.12–1.48)	0.32	0.05	35	1.85 (1.61–2.11)	0.14	<0.01
Cohort	6	1.86 (1.39–2.49)		0.03	5	1.45 (1.20–1.74)		0.86	7	1.51 (1.19–1.91)		0.05
Types of control[d]												
Hospital	21	2.13 (1.77–2.57)	0.15	<0.01	10	1.23 (1.02–1.48)	0.33	0.09	18	1.80 (1.49–2.18)	0.38	<0.01
Population	10	2.57 (2.15–3.07)		0.21	9	1.43 (1.12–1.84)		0.15	16	2.03 (1.69–2.42)		<0.01
Endpoint[e]												
Incidence	6	1.86 (1.39–2.49)	-	0.03	5	1.45 (1.20–1.74)	-	0.86	7	1.51 (1.19–1.91)	-	0.05
Mortality	0	-		-	0	-		-	0			
Year of publication												
≤1995	17	2.55 (2.08–3.14)	0.01	<0.01	12	1.38 (1.16–1.63)	0.70	0.54	15	2.00 (1.64–2.43)	0.24	<0.01
1996–2006	11	1.55 (1.15–2.11)		<0.01	7	1.30 (0.86–1.96)		0.13	13	1.55 (1.14–2.11)		<0.01
≥2007	11	1.90 (1.64–2.20)		0.03	6	1.23 (1.02–1.49)		0.02	14	1.65 (1.41–1.94)		<0.01
Type of lesion												
CIN1	3	1.54 (1.01–2.36)	0.42	0.29	0	-	0.38	-	0	-	0.33	-
CIN 2/3	14	2.02 (1.58–2.57)		<0.01	10	1.20 (1.07–1.33)		0.47	20	1.59 (1.35–1.88)		<0.01
CIN3	13	2.13 (1.70–2.67)		<0.01	9	1.32 (1.09–1.60)		0.17	13	1.81 (1.48–2.22)		<0.01
HPV												
Negative	3	1.94 (1.42–2.65)	0.70	0.44	3	0.93 (0.62–1.39)	0.13	0.28	6	1.50 (1.15–1.94)	0.07	0.35
Positive	3	2.12 (1.55–2.89)		0.61	3	1.53 (0.93–2.51)		0.31	5	2.06 (1.64–2.58)		0.73
HPV adjustment												
No	27	2.28 (1.98–2.64)	0.03	<0.01	20	1.28 (1.14–1.44)	0.72	0.11	30	1.88 (1.66–2.13)	0.08	<0.01
Yes	12	1.59 (1.17–2.15)		<0.01	5	1.42 (0.81–2.50)		0.17	12	1.40 (1.02–1.90)		<0.01
Life partners adjustment												
No	21	1.96 (1.72–2.24)	0.19	<0.01	13	1.33 (1.10–1.61)	0.33	0.05	21	1.80 (1.56–2.07)	0.96	<0.01
Yes	18	2.40 (1.83–3.17)		<0.01	12	1.19 (1.05–1.35)		0.46	21	1.79 (1.46–2.19)		<0.01

CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; RR, relative risk.

[a]*P*-value for heterogeneity across strata.

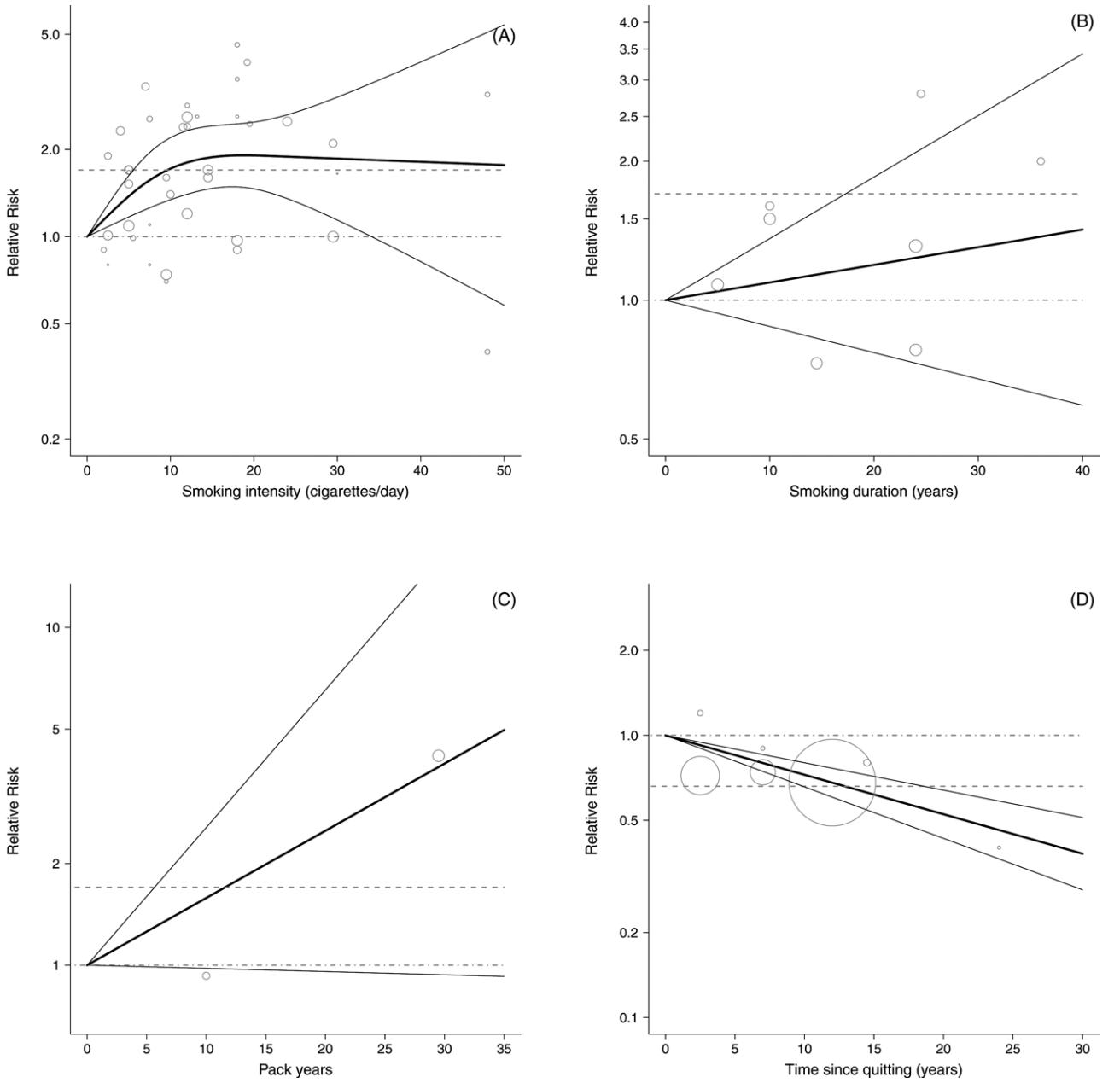
[b]*P*-value for heterogeneity within strata.

[c]Studies in multiple countries from different areas were not included.

[d]Types of control only for case–control studies.

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

Fig. 3

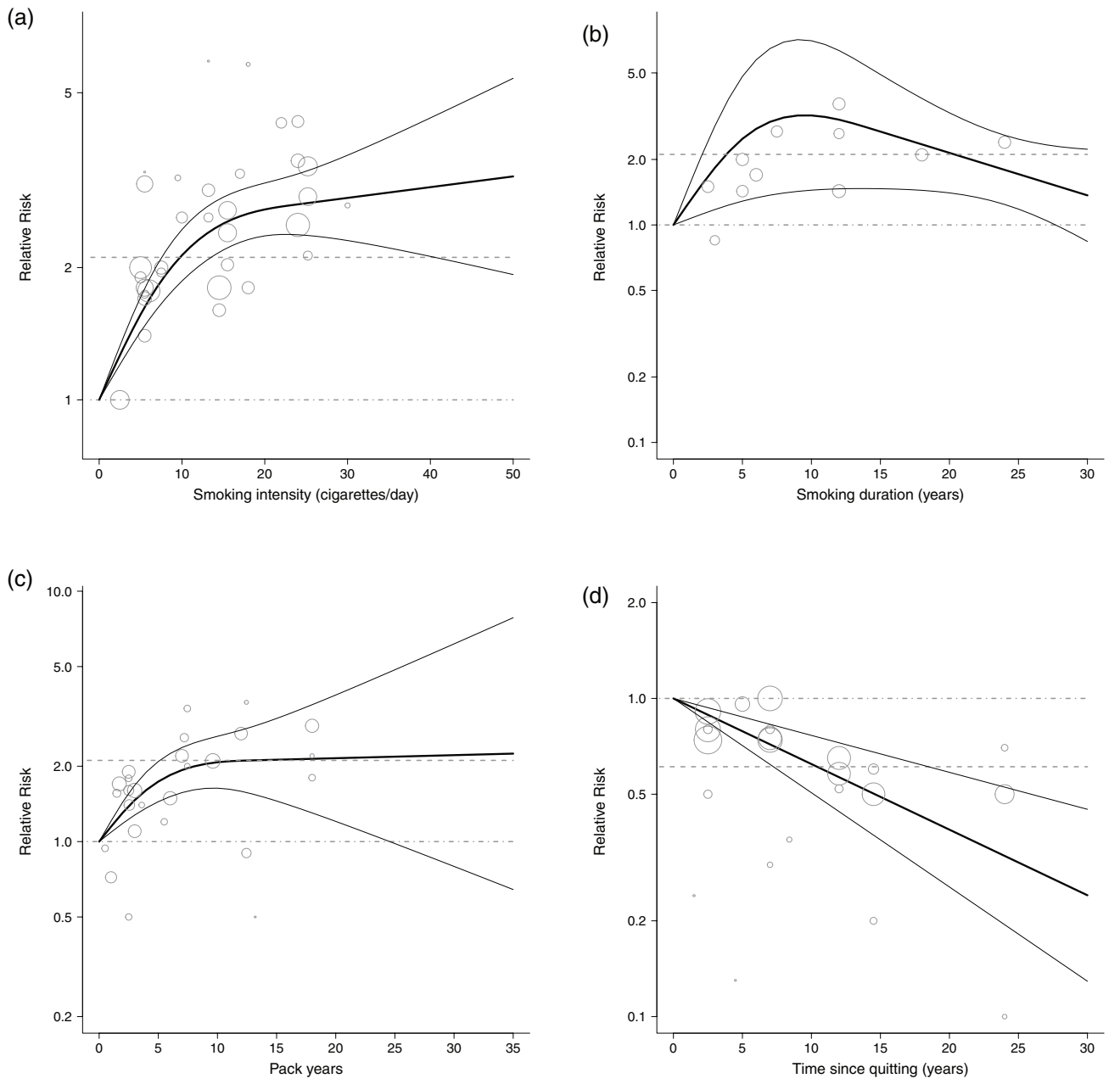


Relative risk (RR) functions describing the dose-response relationships between cigarette smoking intensity, duration, pack-years and time since quitting, and the risk of invasive cervical cancer. (a) Cigarette smoking intensity (based on 15 studies). (b) Cigarette smoking duration (based on three studies). (c) Pack-years (based on one study). (d) Time since quitting (based on two studies). —Restricted cubic spline or linear regression model; –95% confidence interval of the restricted cubic spline or linear model; - - - - RR for the reference category (never smokers in a, b and c, current smokers in d); ○ RR for various exposure categories in each study included in the analysis, where the area of the circle is proportional to the precision of the RR (i.e. to the inverse variance).

CI, 1.72–2.39), even though such review was based on fewer and more recent publications including cross-sectional studies (Nagelhout *et al.*, 2021).

In the present meta-analysis, as in previous studies, the risk of invasive squamous-cell carcinoma was 59% higher for current versus never smokers, whereas no consistent association was observed between smoking and adeno- or adenosquamous-cell carcinoma (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006). Most studies did not report the histologic CC type, though squamous-cell carcinoma is the most frequent, (International Collaboration of

Fig. 4



Relative risk (RR) functions describing the dose-response relationships between cigarette smoking intensity, duration, pack-years and time since quitting, and the risk of preinvasive lesions. (a) Cigarette smoking intensity (based on thirteen studies). (b) Cigarette smoking duration (based on five studies). (c) Pack-years (based on eight studies). (d) Time since quitting (based on seven studies). ─Restricted cubic spline or linear regression model; –95% confidence interval of the restricted cubic spline or linear model; - - - - RR for the reference category (never smokers in a, b and c, current smokers in d); ○ RR for various exposure categories in each study included in the analysis, where the area of the circle is proportional to the precision of the RR (i.e. to the inverse variance).

Epidemiological Studies of Cervical Cancer, 2007) suggesting that results on invasive CC are determined by squamous-cell carcinoma.

To assess the association between smoking and CC, it is important to take into account for the potential confounding effects of HPV infection (Castellsague and Munoz, 2003; Plummer *et al.*, 2003). Even if studies on invasive CC that control for HPV infection are still few (three studies) as well as studies limited to HPV-positive subjects (two and three studies, respectively, on invasive CC and preinvasive lesions), our results showed that taking into account for HPV does not alter either the positive association or its magnitude. These findings confirm that

smoking is an independent risk factor for CC in women infected with oncogenic HPV types (Kapeu *et al.*, 2009), and could support the hypothesis that tobacco smoking facilitates acquisition or persistence of an HPV infection (Vaccarella *et al.*, 2008).

In order to take into account for the spread of screening programmes (occurred on average after 1996) and of HPV vaccination (after 2007), we stratified by year of publication, considering studies conducted before 1995, in 1996–2006, and after 2007. No differences by year of publication were observed, suggesting an association between smoking and CC that is independent from CC preventive programmes.

With reference to the dose-response relationships, we found that, even with few cigarettes per day and few pack-years of smoking, the risk of invasive CC and precancerous lesions was yet high. The risk of precancerous lesions also increased rapidly after few years of smoking duration, whereas the risk of invasive CC showed a slower linear increase. On the other hand, risks of both invasive CC and preinvasive lesions linearly decreased by time since quitting, reaching the risk of never smokers about 15 years since quitting.

The present study shares common limitations of meta-analyses. We pooled data from epidemiological studies conducted in various populations, with different methodologies, including subjects with variable characteristics (e.g. age, race, health condition), and background risk levels, with various definition of smoking, and reporting RRs estimated after allowance of different covariates. However, we set up a series of *a-priori* review rules to exclude possible inconsistencies that may muddle the net effect of smoking on CC; for example, when multiple RRs were reported, only RRs with the most complete list of adjustments were included. We referred, however, to random-effect models to consider such heterogeneity. Moreover, we conducted various stratified analyses to identify possible sources of heterogeneity, although most of the variables considered did not explain the observed heterogeneity. Another limitation common to all meta-analyses is due to the fact that case–control and cohort studies are susceptible to recall and selection biases. In particular, information on cigarette smoking was self-reported in all the included studies. Therefore, some information, particularly smoking intensity and duration, may be misclassified.

The present meta-analysis has several strengths. First, we tried to include as many as possible epidemiologic studies on the issue. To reach this scope, we used an original and innovative approach combining an umbrella review with a traditional systematic review (Lugo *et al.*, 2017). This method was already successfully used in the review and meta-analysis of the association between smoking and other cancer sites (Lugo *et al.*, 2018; Liu *et al.*, 2019; Santucci *et al.*, 2019; Botteri *et al.*, 2020; Lugo *et al.*, 2020). Furthermore, we considered information from publications not indexed in PubMed such as the IARC Monographs (IARC, 2004, 2012b) and the Surgeon General's Report (US Department of Health and Human Services, 2001, 2004). Indeed, we were able to identify several studies that were not captured in previous meta-analyses, although satisfying their inclusion criteria. As an example, in comparison with the IARC Monograph 2012, which included articles up to 2008, our selection up to that date found 41 additional eligible papers, out of which 21 were then not included since they reported results already included in other studies. Second, we carefully screened single-study publications to avoid the inclusion of duplicate results. Third, we estimated the risk functions that best describe the dose-risk relationships with smoking intensity, duration, pack-years and time since quitting, allowing to compute the RR for any level of number of cigarettes, years of use, pack-years smoked, and years since cessation. To our knowledge, no previous meta-analyses on dose-response relationships are available on the issue.

In conclusion, from this comprehensive review and meta-analysis based on an original search design, we can confirm that current and former cigarette smoking was highly associated with both invasive CC and preinvasive lesions. The association of smoking with invasive CC was for invasive squamous-cell carcinoma, whereas no increased risk of adenocarcinoma was observed. This risk rises to over 2 for approximately 20 cigarettes/day or 15 pack-years for invasive CC and approximately 9 cigarettes/day or 8 pack-years for preinvasive lesions and reduces to the risk of never smokers after around 15 years from smoking cessation. The association of smoking with CC was independent from HPV infection and other risk factors, suggesting that smoking habits should be taken in account in clinical practice and in research concerning CC. Finally, the figures given in the present study are important from a public health perspective because they will enable us to exactly quantify the cancer burden attributable to cigarette smoking on both individual and population levels, in order to provide essential information to guide policy decisions for the control of tobacco smoking and cancer prevention.

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S. Gallus and A. Lugo contributed to the study conception and design. Material preparation, data collection and analysis were performed by M.C. Malevolti, M. Scala, A. Lachi and G. Carreras. The first draft of the manuscript was written by G. Carreras and M.C. Malevolti in collaboration with A. Lugo, and all authors commented on previous versions of the manuscript. S. Gallus and G. Gorini supervised the whole work. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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