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Dose-response relationships between cigarette smoking and kidney cancer: A systematic review and meta-analysis

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ABSTRACT

Purpose: We aim to provide the most accurate and updated quantification of the effect of cigarette smoking on kidney cancer risk focusing on dose-response relationships.
Methods: We conducted a meta-analysis, using an innovative approach combining an umbrella review and a traditional literature search.
Results: Fifty-six original studies were included, providing pooled relative risks (RR) of kidney cancer of 1.39 (95% confidence interval, CI: 1.28–1.51) for current and 1.20 (95% CI: 1.14–1.27) for former compared with never smokers. Kidney cancer risk increased non-linearly with smoking intensity, the RR compared with never smokers being 1.18 (95% CI: 1.11–1.26) for five and 1.72 (95% CI: 1.52–1.95) for 30 cigarettes/day, and increased linearly with smoking duration, the RR being 1.70 (95% CI: 1.10–2.64) after 25 years. The risk linearly decreased with time-since-quitting.
Conclusions: Even smoking few cigarettes per day significantly increases kidney cancer risk. Quitting smoking reduces the risk, the earlier the better.

1. Introduction

Tobacco smoking is a widely recognized risk factor for premature morbidity and mortality (GBD 2015 Risk Factors Collaborators, 2016; WHO, 2017), causing more than six million deaths every year worldwide (GBD 2015 Tobacco Collaborators, 2017). The International Agency for Research on Cancer (IARC) listed up to 15 cancers, including kidney cancer, causally related to smoking, establishing tobacco smoke as a multiple-organ-site carcinogen (IARC, 2012).

Kidney cancer is the 13th most common cancer and the 16th most common cause of cancer death worldwide, with about 338,000 new cases and 144,000 deaths each year (Ferlay et al., 2013, 2015). Its incidence and mortality rank higher in Europe, North America, Australia/New Zealand, and Japan (Scelo and Larose, 2018). Renal cell carcinoma is the most common type of kidney cancer, accounting for 90% of renal tumours (Eble et al., 2004). Although the aetiology of kidney cancer is largely unknown, various factors have been associated with the risk of kidney cancer, including obesity, smoking, hypertension, chronic kidney disease, exposure to certain toxic substances, and family history of kidney cancer (Scelo and Larose, 2018; American Cancer Society, 2018). In particular, smoking represents one of the known risk factors with a high attributable proportion of kidney cancer cases (i.e., 18–30%) (Benichou et al., 1998; McLaughlin et al., 2006; Cumberbatch et al., 2016).

At least three systematic reviews and meta-analyses have been conducted on the issue so far (Cumberbatch et al., 2016; Hunt et al., 2005; Gandini et al., 2008). The most recent and well-conducted meta-analysis combined data from 31 studies published up to 2013 and found pooled relative risk (RR) of renal cell cancer of 1.36 (95% confidence interval, CI: 1.19-1.56; based on 18 studies) for current, and 1.16 (95% CI: 1.08–1.25, based on 18 studies) for former smokers compared with never smokers (Cumberbatch et al., 2016). To our knowledge, neither this meta-analysis nor other previous ones comprehensively investigated the dose-response relationships between smoking intensity, duration, and time since quitting and the risk of kidney cancer.

To obtain an accurate and updated quantification of the association

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between cigarette smoking and kidney cancer risk, and to provide the functions that best describe the dose-response relationships, we conducted a comprehensive review and meta-analysis of available epidemiological studies on the effect of cigarette smoking on the risk of kidney cancer. The review and meta-analysis was conducted using an innovative methodology for the identification of original publications, which combines umbrella and traditional reviews (Lugo et al., 2017).

2. Materials and methods

The present systematic review and meta-analysis was conducted following the methodology described in detail in previous publications (Lugo et al., 2017, 2018). Its protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017063991).

In a first step, we conducted an umbrella review (Aromataris et al., 2015) on smoking and the risk of cancer at any site. Umbrella reviews provide syntheses of existing evidence on a specific topic, systematically searching and evaluating all multiple systematic reviews and/or meta-analyses on all health outcomes associated with a specific exposure (Aromataris et al., 2015). 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), following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement, we identified all meta-analyses, pooled analyses, and reviews on the association between cigarette smoking and the risk of cancer at any site published before 27th April 2017 (Lugo et al., 2017). Out of 175 eligible articles, we identified five systematic reviews/meta-analyses (Cumberbatch et al., 2016; Gandini et al., 2008; Dhote et al., 2000; Nakamura et al., 2009), and one pooled analysis (Katanoda et al., 2008) reporting data on kidney cancer (Fig. 1). Additionally, we considered two monographs of IARC on tobacco smoking (IARC, 2004, 2012). We screened the eight above mentioned reports and identified a total of 58 non-duplicate articles on tobacco smoking and the risk of kidney cancer.

In a second step, we carried out an updated literature search to identify all original studies on the issue published between 1 January 2013 (i.e., the year of conduction of the last and most comprehensive review available on the issue (Cumberbatch et al., 2016)) and 30th November 2017 (**Supplementary Box 1**). After the exclusion of ineligible articles – eligibility independently assessed by two reviewers (XL and AL) - and duplicate publications, and the inclusion of additional publications identified from other sources, the updated literature search resulted in 17 original publications on cigarette smoking and the risk of kidney cancer. Combining original articles identified in the umbrella review and in the update, we retrieved 75 relevant original study publications that were screened for eligibility on the basis of their full text (Fig. 1). Discrepancies between the two were solved with the help of a third reviewer (SG).

Studies were included in the present meta-analysis if they satisfied all of the following eligibility criteria: i) 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) published as original articles in English; iii) provide data on the general human population; iv) provide information on cigarette smoking; v) report risk estimates, including risk ratios, odds ratios, hazard ratios or mortality rate ratios – all referred to as RR – for at least one variable among smoking status (current, former and/or ever smoking), intensity, duration and time since quitting, as compared to never or current cigarette smokers, and corresponding

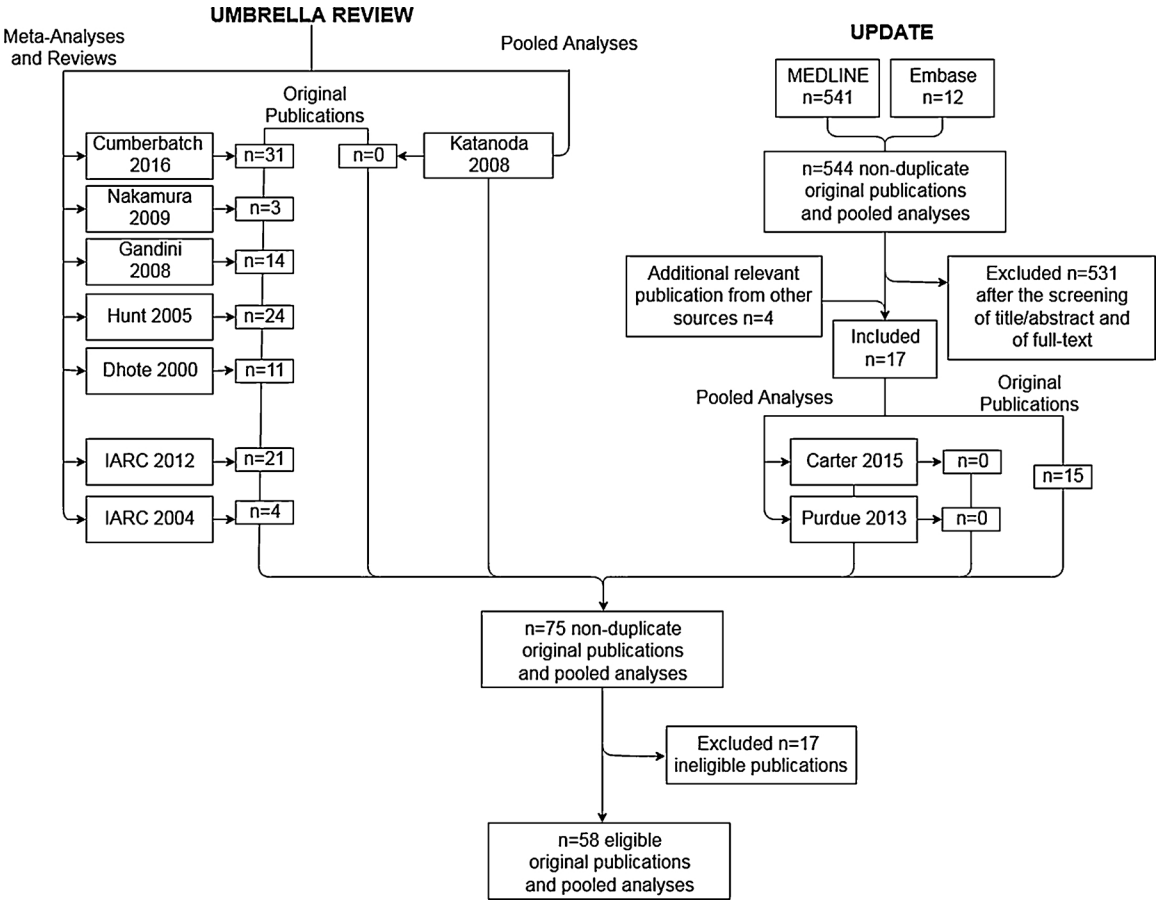

Fig. 1. Flowchart for the selection of the original studies on the association between cigarette smoking and kidney cancer risk included in the review and meta-analysis.

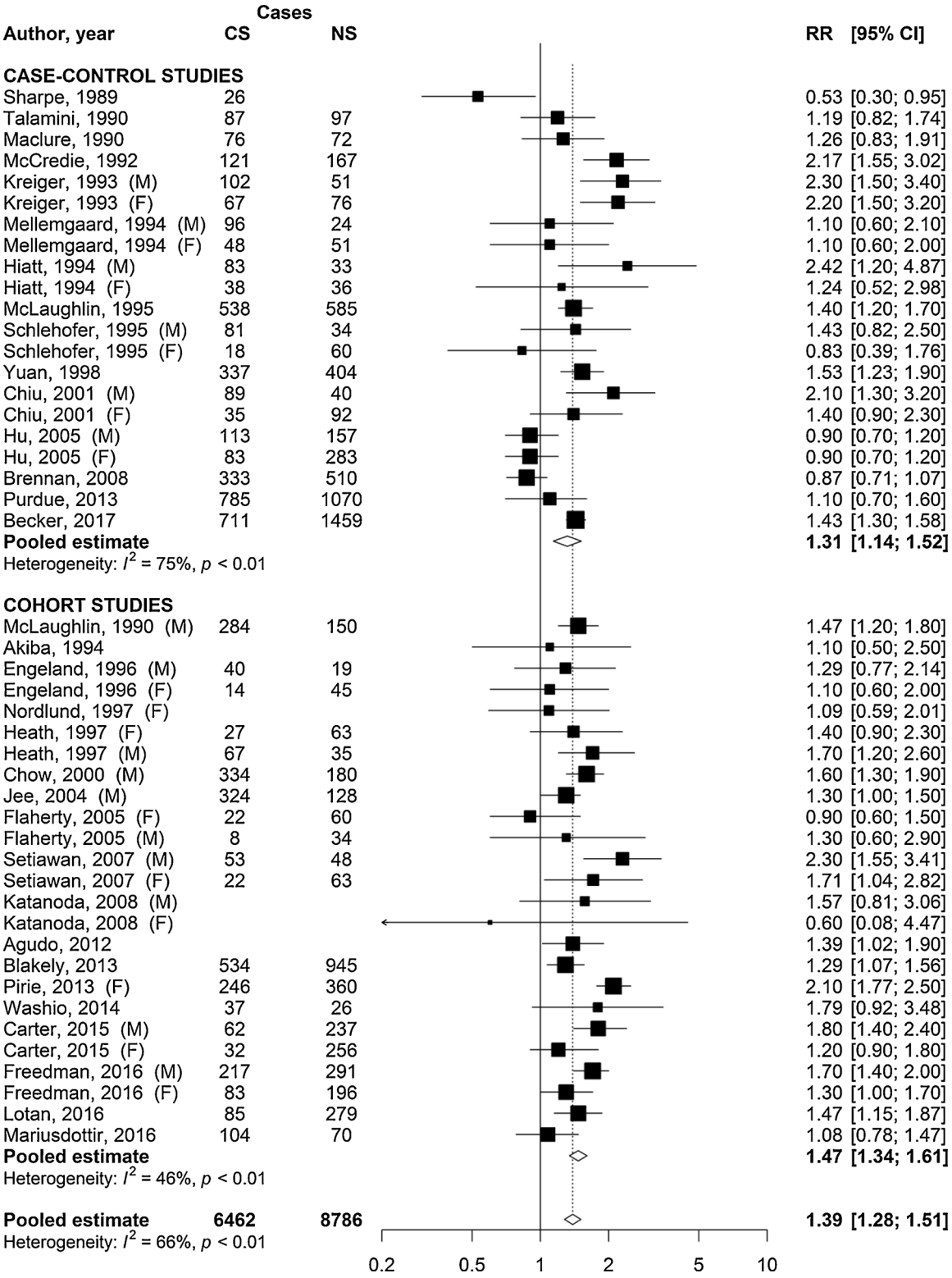

Fig. 2. Forest plot for study-specific and pooled relative risk (RR) of kidney cancer for current cigarette smokers vs. never smokers, overall and by study design. Footnote:M: males; F: females; CI: confidence interval; CS: current cigarette smokers among cases; NS: never cigarette smokers among cases.

95% CIs or providing sufficient information to compute them. When results of the same study were provided in more than one original publications, we considered data published in the most recent and/or complete article.

Out of the 75 articles retrieved, 58 met the above mentioned eligibility criteria (Fig. 1; **Supplementary Table 1**).

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, outcome and sample size), model used for RR estimates (including covariates allowed for), and the RR estimates with the corresponding 95% CIs and, when available, the number of cases and controls (or subjects at risk/person

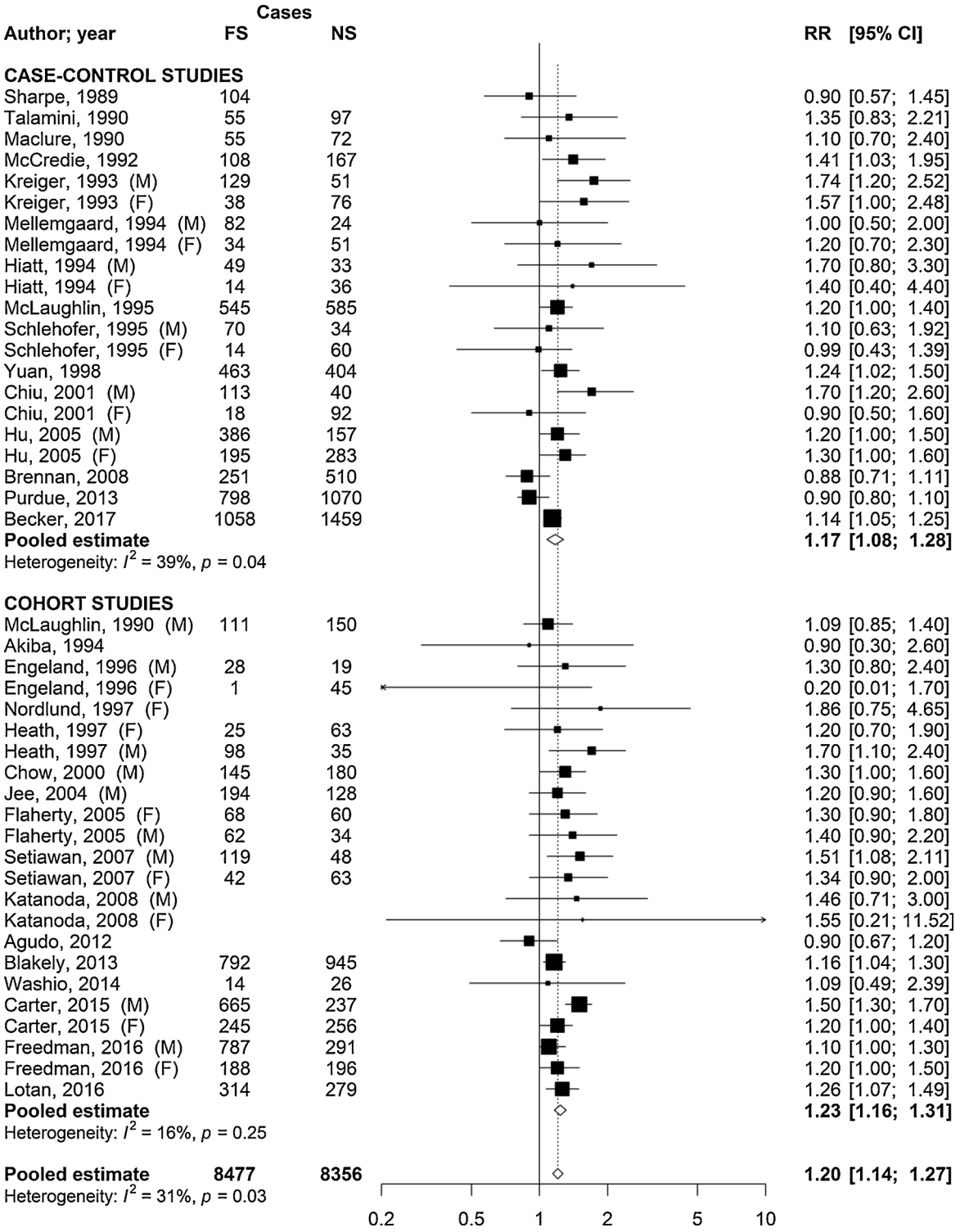

Fig. 3. Forest plot for study-specific and pooled relative risk (RR) of kidney cancer for former cigarette smokers vs. never smokers, overall and by study design. Footnote: M: males; F: females; CI: confidence interval; FS: former cigarette smokers among cases; NS: never cigarette smokers among cases.

years for cohort studies) for various exposure categories.

When necessary, we used the method for pooling non-independent estimates described by Hamling and colleagues (Hamling et al., 2008) to change the reference category or to collapse the RRs of two or more categories when the reference group was the same.

We estimated the pooled RRs for current, former and ever smokers, overall and separately in case-control and cohort studies, 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). We further conducted stratified analyses based on various study and population characteristics, including sex, geographic area, income group, type of controls (for case-control studies), endpoint (for cohort studies), and year of publication.

Table 1
Pooled relative risks (RR) and corresponding 95% confidence intervals (CI) of kidney cancer risk for current, former, and ever cigarette smokers versus 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[a]	p-value[b]	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]
Total	33	1.39 (1.28-1.51)	< 0.01		31	1.20 (1.14-1.27)	0.03		51	1.26 (1.19-1.33)	< 0.01	
Sex												
Men	20	1.57 (1.38-1.77)	< 0.01	0.06	20	1.29 (1.18-1.41)	0.04	0.26	28	1.38 (1.27-1.50)	< 0.01	0.02
Women	19	1.27 (1.06-1.51)	< 0.01		18	1.20 (1.10-1.31)	0.86		23	1.21 (1.12-1.31)	0.32	
Geographic area[c]												
North America	14	1.44 (1.27-1.64)	< 0.01	0.61	14	1.28 (1.20-1.36)	0.22	0.09	27	1.30 (1.21-1.40)	< 0.01	0.50
Europe	11	1.28 (1.09-1.51)	< 0.01		9	1.10 (1.00-1.21)	0.33		13	1.19 (1.08-1.31)	0.03	
Asia	4	1.33 (1.11-1.59)	0.76		4	1.20 (0.94-1.54)	0.95		6	1.26 (1.08-1.47)	0.47	
Oceania	2	1.64 (0.99-2.73)	–		2	1.20 (1.04-1.40)	0.26		3	1.35 (1.07-1.71)	0.01	
Income group												
High income	32	1.40 (1.28-1.52)	< 0.01	–	30	1.22 (1.16-1.28)	0.19	–	47	1.27 (1.21-1.32)	< 0.01	0.79
Middle income	0				0	–	–		3	1.35 (0.85-2.14)	0.09	
Type of controls[d]												
Hospital	4	1.00 (0.69-1.45)	< 0.01	0.14	4	1.05 (0.87-1.25)	0.12	< 0.01	8	1.12 (0.99-1.26)	< 0.01	< 0.01
Population	10	1.44 (1.21-1.71)	< 0.01		10	1.27 (1.17-1.38)	0.77		20	1.32 (1.18-1.48)	< 0.01	
Endpoint[e]												
Incidence	12	1.40 (1.27-1.54)	0.09	0.34	11	1.19 (1.12-1.26)	0.58	0.09	16	1.25 (1.19-1.32)	0.69	0.07
Mortality	7	1.54 (1.29-1.83)	0.02		6	1.32 (1.18-1.47)	0.33		7	1.37 (1.27-1.49)	0.41	
Year of publication												
≤1999	15	1.43 (1.26-1.62)	0.01	0.54	15	1.25 (1.15-1.36)	0.74	0.38	25	1.35 (1.24-1.47)	0.07	0.14
2000-2009	8	1.29 (1.05-1.57)	< 0.01		8	1.24 (1.12-1.37)	0.23		12	1.23 (1.06-1.43)	< 0.01	
≥2010	10	1.46 (1.31-1.64)	< 0.01		8	1.15 (1.05-1.26)	< 0.01		14	1.22 (1.14-1.29)	0.02	

[a] p-value for heterogeneity within strata.
[b] p-value for heterogeneity across strata.
[c] Studies conducted in multiple countries from different geographic areas were not included.
[d] Type of controls for case-control studies only. Pooled analyses considering both studies with hospital and with population controls were not included.
[e] Endpoint for cohort studies only. Studies providing RRs for both incidence and mortality were considered in both categories.

To evaluate 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 association between smoking intensity (for current vs. never smokers), duration (for current vs. never smokers), and time since quitting (for former vs. current smokers), and the log relative risk of kidney cancer. For each exposure variable, we tested the log-linearity using the Wald test. Nonlinear relationships between smoking intensity and log RR of kidney cancer were evaluated using a one-stage random-effects dose-response model (Crippa et al., 2019). We modeled smoking intensity using restricted cubic spline with three knots at its fixed percentiles (10%, 50%, and 90%) (Desquilbet and Mariotti, 2010) (**Supplementary Box 2A**). For each exposure category, the level of exposure was assigned as the midpoint between the upper and the lower bound of the category; for open-ended upper categories, the level of exposure was determined as 1.2 times the lower bound (Lugo et al., 2017; Bagnardi et al., 2015; Berlin et al., 1993). When the number of cases and/or controls in one or more exposure categories was not provided in the original study publication, we considered the total number of cases and/or controls in the study weighted by the average percent distribution of subjects pooled from all other studies, in order to estimate the covariance among the log RR (Crippa and Orsini, 2016).

All statistical analyses were performed using the R-software version 3.4.1 (R Development Core Team, 2017), and, in particular, the "*meta*" and "*dosresmeta*" packages (Crippa and Orsini, 2016).

The main findings of the meta-analysis will be published in a dedicated website (www.epideuro.eu), where additional data could be provided to keep the meta-analysis updated.

3. Results

Out of the 58 eligible articles, two were excluded since their data were included in other publications (**Supplementary Table 1**). Thus, 56 articles were included in the present meta-analysis.

Supplementary Table 2 and **Supplementary Table 3** summarize the main characteristics of the included case-control (N = 32) and cohort (N = 24) studies, respectively. The original articles were published between 1958 and 2017 and were based on a total of 25,751 kidney cancer cases. Thirty-three studies provided a measure of association – or information to derive it – for current smokers, 31 for former smokers, and 51 for ever smokers, as compared to never smokers. Moreover, 17 studies reported RR estimates for smoking intensity (13 among current smokers), 10 for smoking duration (2 among current smokers), and 10 for time since quitting smoking.

Supplementary Table 4 shows the list of publications for which data have been partially excluded from the meta-analysis, with the corresponding reasons of exclusion.

Fig. 2 gives the study-specific and pooled RRs of kidney cancer for current vs. never cigarette smokers. The pooled RR was 1.39 (95% CI: 1.28–1.51) in all studies combined; the corresponding estimates were 1.31 (95% CI: 1.14–1.52) in case-control studies and 1.47 (95% CI: 1.34–1.61) in cohort studies. For all pooled estimates, there was significant between-study heterogeneity ($p < 0.01$).

The pooled RR of kidney cancer for former vs. never cigarette smokers was 1.20 (95% CI: 1.14–1.27) in all studies combined; the corresponding estimates were 1.17 (95% CI: 1.08–1.28) in case-control studies and 1.23 (95% CI: 1.16–1.31) in cohort studies (Fig. 3). There was significant between-study heterogeneity overall ($p = 0.03$) and among case-control studies ($p = 0.04$), but not among cohort studies ($p = 0.25$).

The pooled RR of kidney cancer for ever vs. never cigarette smokers was 1.26 (95% CI: 1.19–1.33) overall, 1.24 (95% CI: 1.14–1.34) in case-control studies, and 1.29 (95% CI: 1.23–1.35) in cohort studies (**Supplementary Fig. 1**). There was significant between-study heterogeneity overall ($p < 0.01$) and among case-control studies ($p < 0.01$), but not among cohort studies ($p = 0.48$).

No significant differences in the risk of kidney cancer were observed

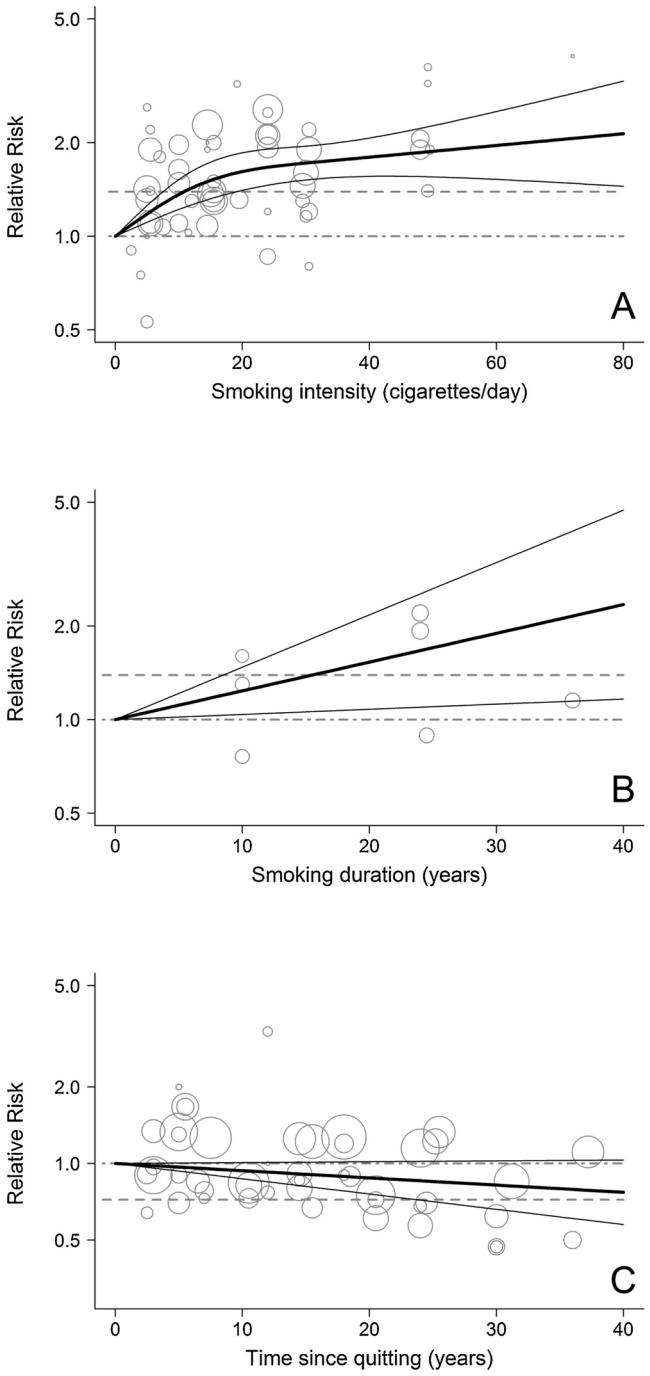

Fig. 4. Relative risk (RR) functions describing the dose-response relationships between cigarette smoking intensity, duration, and time since quitting and kidney cancer risk. Footnote: A: Cigarette smoking intensity (based on 13 studies); B: cigarette smoking duration (based on 2 studies); C: time since quitting (based on 10 studies). ——— Smoking intensity (A): restricted cubic spline from a random-effects dose-response model; smoking duration (B) and time since quitting (C): linear model. ——— 95% confidence interval of the spline (A) and linear (B and C) model; - - - - RR for current vs. never cigarette smokers (A and B), or for never vs. current cigarette smokers (C); - · - · RR for the reference category (never smokers in A and B, current smokers in C); ○ RR for various exposure categories in each study included in the analysis, where the area of the circle is proportional to the precision (i.e., to the inverse variance) of the RR.

for current, former, and ever smokers based on study design, geographic area, income group, endpoint (in cohort studies), and year of publication (Table 1). For ever smokers, the risk of kidney cancer was significantly different between males (RR = 1.38) and females (RR = 1.21; p for heterogeneity across strata = 0.02). When considering only case-control studies, a significant difference was observed across type of controls for former smokers (RRs were 1.05 for hospital and 1.27 for population controls; $p < 0.01$) and for ever smokers (RRs were 1.12 for hospital and 1.32 for population controls; $p < 0.01$).

No evidence of publication bias was found for current, former, and ever smokers either from the visual inspection of the funnel plots (**Supplementary** Figs. 2–4, respectively) or from the Egger's test (p = 0.376, 0.358, and 0.271 for current, former, and ever smokers, respectively).

Fig. 4 shows the dose-response relationships between smoking intensity (**Panel A**), duration (**Panel B**), and time since quitting (**Panel C**), and the risk of kidney cancer. We observed a nonlinear increase in kidney cancer risk with smoking intensity, with the risk sharply increasing even at a low number of cigarettes up to 30 cigarettes/day, and slightly growing at higher numbers of cigarettes/day. The RRs were 1.18 (95% CI: 1.11–1.26) for five, 1.36 (95% CI: 1.22–1.52) for ten, 1.61 (95% CI: 1.40–1.86) for 20, and 1.72 (95% CI: 1.52–1.95) for 30 cigarettes/day (estimated using the curve function in **Supplementary Box 2B**). The risk of kidney cancer demonstrated a significant linear increase with duration of the habit: the RRs were 1.24 (95% CI: 1.04–1.47) for 10 years of smoking and 1.70 (95% CI: 1.10–2.64) for 25 years of smoking (estimated using the linear function in **Supplementary Box 2B**), although the duration-risk curve was based on two studies only. We were able to confirm the linearity of the dose-response relationship with duration for ever smokers (based on 9 studies; **Supplementary Figure 5**). Kidney cancer risk linearly decreased with time since quitting cigarette smoking, with RRs for former vs. current smokers being 0.94 (95% CI: 0.87–1.01) for 10 years of quitting, 0.88 (95% CI: 0.76–1.02) for 20 years of quitting, and 0.82 (95% CI: 0.66–1.02) for 30 years of quitting however, without reaching the same level as never smokers (RR for never vs. current smokers is 0.72, 95% CI: 0.66-0.78).

4. Discussion

In this comprehensive review and meta-analysis conducted using an original design, we summarized the available evidence from 56 epidemiological studies - out of 58 eligible ones - confirming a significant association between cigarette smoking and the risk of kidney cancer. We found an increased risk of kidney cancer of 39% in current smokers, 20% in former smokers, and 26% in ever smokers as compared to never smokers. In particular, we observed a nonlinear dose-response relationship with smoking intensity, the risk of kidney cancer sharply increasing at a relatively few cigarettes per day, and a linear dose-response association with duration and time since quitting.

Consistent risk estimates were found between case-control and cohort studies, across strata of other characteristics, i.e., geographic area, endpoint evaluated, and year of publication. However, as previously reported (Hunt et al., 2005), we found a significantly higher risk of kidney cancer among male ever smokers as compared to female ones. This could be due to fact that man have higher predisposition to hypertension, which is a major recognized risk factor of kidney cancer (Maranon and Reckelhoff, 2013). Moreover, hormones may play a role in such difference, by regulating the renin-angiotensin system (Reckelhoff, 2001) and modulating the risk of kidney diseases (Yanes et al., 2008) in different ways between men and women. Moreover, we observed higher RRs for former and ever smokers in population-based rather than hospital-based case-control studies. Again this was already observed in a previous meta-analysis (Hunt et al., 2005) and it is possibly due to a lower frequency of smoking among the general population than in hospital controls (Rothman et al., 2012).

Three meta-analyses focusing on smoking as a risk factor for kidney cancer – based on 15 (Gandini et al., 2008), 24 (Hunt et al., 2005), and 31 (Cumberbatch et al., 2016) studies, respectively – have been previously published. They reported RRs between 1.36 (Cumberbatch et al., 2016) and 1.52 (Gandini et al., 2008) for current smokers, 1.16

(Cumberbatch et al., 2016) and 1.25 (Gandini et al., 2008) for former smokers, and 1.38 (Hunt et al., 2005) and 1.45 for ever smokers (Cumberbatch et al., 2016). The RRs reported in these studies are in line with our estimates, although there are slight differences, which could be, at least partially, caused by different inclusion criteria of publications, literature search strategies, and different calendar periods of conduction. We believe that, by careful screening and inclusion of the most updated data and recent studies, our study provides a more precise estimation of the effect of smoking on kidney cancer risk. Indeed, we considered 58 eligible studies, almost twice the number of the most comprehensive meta-analysis previously conducted (n = 31) (Cumberbatch et al., 2016), including a few recent publications, mainly from cohort studies with a large sample size.

We found a nonlinear increase in the risk of kidney cancer with smoking intensity among current smokers, with a sharp increase in risk at relatively low smoking intensities. Smoking only 5 cigarettes/day significantly increased the risk by 18%, and 10 cigarettes/day by 36%. Moreover, we observed a slower increase in the risk of kidney cancer even at high smoking intensity. This is somewhat different from the dose-response relationships previously reported for lung, bladder cancer (Vineis et al., 2000), and pancreatic cancer (Lugo et al., 2018), where the association levelled off at high smoking intensities. This finding suggests that the sensitivity to smoking impact among heavy smokers does not decrease significantly as compared to light smokers. Nevertheless, it should be noted that due to the heterogeneity in the methods used to determine smoking intensity, and the limited readings of original RR available for a robust estimation (as indicated by the large CIs of those estimates), the dose-risk curves after intensity of 30 cigarette per day should be interpreted with caution. For the same reasons, the estimation of risk following smoking duration and after 30 years after quitting should also be interpreted with caution.

Previous evidence indicated that the susceptibility to kidney cancer due to smoking is associated with genetic mutations on chromosome 3p (Zhu et al., 2008). The von Hippel-Lindau gene on chromosome 3p has been identified as one of the first and most frequent sites of mutagenesis in both sporadic and familial renal cell carcinoma (Koul et al., 2011). However, it has also been shown that smoking does not increase mutations in this gene (van Dijk et al., 2006), while smoking-induced mutations in p53 can be associated with kidney cancer in both humans and experimental models (Kroeger et al., 2012; Ganguly et al., 2018). Recently, it has been shown that smoking is associated with DNA hypomethylation that reflects genomic instability and can lead to the development of kidney cancer (Mendoza-Perez et al., 2016).

In addition to mutagenic activity of the compounds contained in the smoke, other mechanisms have been identified. In particular, the generation of oxygen radicals and oxidative DNA damage may be involved in the onset of smoking-induced kidney cancer (Kabaria et al., 2016; Guo et al., 2014; Arany et al., 2012; Clague et al., 2009).

Although the mechanisms underlying the induction of kidney cancer by smoking have not yet been fully clarified, several studies have shown that prolonged exposure to nicotine increases AKT and angiogenesis, thus favoring proliferation and growth of kidney cancer (Heeschen et al., 2001). More recently, it has been shown that smoking is able to favor the metastasization of renal tumor cells through the regulation of some metalloproteases (Ishida et al., 2015), as well as to favor the tumor growth by supporting the renal tumor stem cell pool (Qian et al., 2018).

Our present study shares the limitations common to all meta-analyses. We pooled data from epidemiological studies conducted in various populations, with different methodologies, including subjects with variable characteristics (e.g., sex, age, race, health condition) and background risk levels, with various definition of smoking, and reporting RRs estimated after allowance of different covariates. This may explain some of the heterogeneity observed between studies. However, we set up a series of review rules *a priori* to exclude possible inconsistencies that may muddle the net effect of smoking on kidney cancer; for example, when multiple RRs were reported, only RRs with the most complete list of adjustments were included; we referred to random-effect models to take into account 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 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.

Our meta-analysis has also many strengths. To provide a comprehensive estimation of the effect of smoking on the risk of kidney cancer, we aimed at including as many epidemiologic studies as possible. We used an innovative approach that combines an umbrella review with the traditional systematic review (Lugo et al., 2017); we considered not only publications indexed in PubMed and/or Embase, but also all the publications on the issue reported by the IARC Monographs (IARC, 2004, 2012). Meanwhile, we built strict eligibility criteria and carefully screened every publication to avoid the inclusion of results that were later on reported by other publications. Moreover, we excluded studies based on subjects in the comparison group who unlikely represent the general population, e.g. patients with other cancers, other severe diseases or smoking related diseases. In addition, the main strength of the study is that we estimated the risk functions which best describe the dose-risk relationships with smoking intensity, duration, and time since quitting smoking, allowing for the computation of RR for any level of number of cigarettes, smoking duration, and years since cessation (Crippa and Orsini, 2016; Orsini et al., 2012).

The studies included in our meta-analyses were of different study quality, however, we decided not to exclude *a priori* any study for design weakness or data quality, as one of the aims of our study is to provide the most complete and comprehensive database to be used for further consideration and interpretation.

5. Conclusions

In conclusion, the present comprehensive review and meta-analysis provides the most accurate and updated evidence of a nonlinear relationship between kidney cancer risk with intensity of smoking and allows estimation of long-term effect of smoking intensity, duration, and time since quitting smoking. It confirms that smoking increases the risk of kidney cancer by around 40%, the risk continuously increasing with smoking intensity and duration. Among former smokers, the risk of kidney cancer was 20% higher. Quitting smoking cannot bring down completely the risk to the level of never smokers; hence, it is essential that never smokers avoid smoking in the very first place, smokers quit smoking and, quit smoking as soon as possible for an effective cancer prevention.

Data sharing information

Data included in the meta-analyses will be freely available online at: www.epideuro.eu.

Authors' contributions

SG and AL had the original idea of the work and designed the innovative methodology for the identification of original publications. XL and AL identified the articles, XL extracted the data, XL, GP and AL performed the statistical analyses, with the help of SG. XL drafted the manuscript. All authors contributed to critical review, revising the manuscript draft, and approved the final version.

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Declaration of Competing Interest

The authors have no potential conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.07.019.

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