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Renal cell carcinoma in relation to cigarette smoking: Meta-analysis of 24 studies

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Renal cell carcinoma (RCC) accounts for 3% of adult deaths from cancer. The risk factors for its development are still under intense investigation. Although tobacco smoke is a risk factor, the data are inconsistent and the extent of the increased risk is unclear. Estimates from 19 case-control and 5 cohort studies were used. The case-control reports included 8,032 cases and 13,800 controls; the cohort estimates were based on 1,457,754 participants with 1,326 cases of RCC. The relative risk (RR) for RCC for ever smokers as compared to lifetime never smokers was 1.38 (95% confidence interval [CI] = 1.27–1.50). The RR for male smokers was 1.54 (95% CI = 1.42–1.68) and for female smokers was 1.22 (95% CI = 1.09–1.36). For men and women there was a strong dose-dependent increase in risk. Ever smoker men who had smoked 1–9, 10–20 or 21 or more cigarettes/day had a RR of 1.60 (95% CI = 1.21–2.12), 1.83 (95% CI = 1.30–2.57), or 2.03 (95% CI = 1.51–2.74), respectively. For women, the relative risks were 0.98 (95% CI = 0.71–1.35), 1.38 (95% CI = 0.90–2.11), or 1.58 (95% CI = 1.14–2.20), respectively. The advantages of smoking cessation were confirmed by a reduction in RR for those who had quit smoking for >10 years as compared to those who had quit for 1–10 years. Inhaled tobacco smoke is clearly implicated in the etiology of RCC, with a strong dose-dependent increase in risk associated with numbers of cigarettes smoked per day and a substantial reduction in risk for long-term former smokers.

Key words: kidney cancer; RCC; tobacco; primary tobacco smoke; tobacco dose-response; smoking cessation

Cancers of the kidney comprise a heterogeneous class of tumors arising from several different cell types within the nephron and are classified into 4 subgroups (all under ICD-O C64): renal cell carcinoma (RCC, also called clear cell carcinoma or non-papillary carcinoma), papillary renal cell carcinoma (also called chromophilic renal cell carcinoma), chromophobe renal cell carcinoma and unclassified renal cell carcinoma. Excluded from this list are transitional cell carcinomas of the renal pelvis (C65), which are histologically comparable to bladder cancers (C67) and seem to share a common etiology.[1,2] Adenocarcinoma of the renal pelvis is rare.[3]

Despite numerous case-control and prospective cohort studies addressing the etiology of RCC dating to the late 1950s, the risk factors are still poorly understood.[4] The risk from tobacco smoking has been evaluated in hospital-based case-control studies,[5–13] a registry-based case-control study,[14] population-based case-control studies[15–29] and prospective cohort studies[30–41] (summarized in Tables I,II). In 1982 and again in 1990, the U.S. Surgeon General fell short of concluding that cigarette smoking was a cause of RCC, but instead reported that cigarette smoking was a contributing factor in the etiology of RCC.[42,43] In 2002, an International Agency for Research on Cancer (IARC) Working Group was convened to update a previous IARC monograph on tobacco smoking published in 1986.[44] They concluded that tobacco smoking was a risk factor for RCC.[45,46] To date, however, a systematic evaluation of the RR for developing RCC from cigarette smoking has not been reported. Although it is now clear that cigarette smoking is a cause of RCC, the level of risk and the benefits of smoking cessation remains uncertain. Our report is the most precise and comprehensive estimate of the carcinogenic effect of tobacco smoke on RCC.

Subjects and methods

Data collection and selection of studies included in the meta-analysis

A comprehensive review of the literature was carried out to identify all available estimates of the risks for RCC associated with cigarette smoking. Identification of published studies was initially conducted using PubMed and was expanded by a review of previously cited references. To limit publication bias, search criteria were not limited to "kidney cancer" and "tobacco," but instead to "kidney cancer" and all suspected risk factors: "tobacco smoke, socio-economic status, body mass index (obesity), hypertension, diuretic use, consumption of coffee, animal proteins, alcohol, or milk, and occupation." Only studies that specifically addressed the risk of RCC (ICD-8 189.0, ICD-9 189.0, or ICD-10 C64) were selected for this meta-analysis. Those studies that included risks associated with all kidney cancers (ICD-6 code 180 or ICD-7 code 180), with carcinoma of the renal pelvis (ICD-8 code 189.1, ICD-9 code 189.1, or ICD-10 code C65), or that did not specifically provide an ICD code were excluded from the meta-analysis estimates.[12,35–40] Cohort studies that were earlier reports published later with longer follow-up[41] or case-control studies that were reported more than once[13,18,22,28,29] were excluded from the meta-analysis. The case-control studies that were used in the meta-analysis were published between 1968–2003 (including data from a combined 8,032 cases and 13,800 controls). The cohort studies that were used in the meta-analysis were published between 1990–2004 (including 1,457,754 individuals involving 1,326 cases of RCC).

For each study, data were abstracted for study type (case-control or cohort), control matching criterion (individual or frequency), the date of publication, the region from which the study participants were recruited (Asia, Australia, Europe, North America or Multi-Region), gender (male, female or combined), smoking status (ever, former, current), number of cases and controls, size of the cohort, years of follow-up of the cohort and RR (with corresponding 95% CI). As summarized in Table III, the adjusted risks associated with cigarette smoking were reported in a variety of ways including stratification by gender or smoking status. To limit the heterogeneity induced by multiple adjustment criteria, the crude RR with corresponding 95% CI and standard error (SE) were calculated from abstracted published data when possible (Table III). The published adjusted risks and the calculated RR were used in separate meta-analyses as appropriate. Several studies did not report an RR for ever smokers. For these studies, a summary estimate for ever smokers was generated using reported RR for each gender and for each smoking category. This summary estimate was used in the meta-analysis for calculation of the overall RR for ever smokers.

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TABLE I – CASE-CONTROL STUDIES USED IN META-ANALYSIS ESTIMATES

Reference[1]	Control type	Matching	Cases	Controls	Region
Bennington and Laubscher, 1968[5]	Hospital	Individual	100	190	North America
Wynder *et al.,* 1974[6]	Hospital	Individual	202	394	North America
Armstrong *et al.,* 1976[7]	Hospital	Individual	106	139	Europe
Goodman *et al.,* 1986[8]	Hospital	Individual	267	267	North America
Talamini *et al.,* 1990[9]	Hospital	Individual	240	665	Europe
Benhamou *et al.,* 1993[10]	Hospital	Individual	196	347	Europe
Muscat *et al.,* 1995[11]	Hospital	Frequency	788	779	North America
Brownson, 1988[14]	Registry[2]	Frequency	326	978	North America
McLaughlin *et al.,* 1984[15]	Population	Frequency	506	714	North America
Yu *et al.,* 1986[16]	Population	Individual	160	160	North America
Maclure and Willett, 1990[17]	Population	Individual	410	605	North America
Finkle *et al.,* 1993[19]	Population	Individual	191	191	North America
Kreiger *et al.,* 1993[20]	Population	Frequency	518	1,381	North America
Hiatt *et al.,* 1994[21]	Population	Individual	257	257	North America
McLaughlin *et al.,* 1993[23]	Population	Frequency	1,732	2,309	Australia, Europe, North America
Yuan *et al.,* 1998[24]	Population	Individual	1,204	1,204	North America
Chiu *et al.,* 2001[25]	Population	Frequency	406	2,336	North America
Semenza *et al.,* 2001[26]	Population	None	115	259	North America
Menezes *et al.,* 2003[27]	Population	None	308	625	North America

[1]Superscripts in this column are references.–[2]Controls were selected from patients in the Missouri Cancer Registry diagnosed with non-tobacco-related cancers.

TABLE II – COHORT STUDIES USED IN META-ANALYSIS ESTIMATES

Reference[1]	Size of cohort	Gender	Follow-up	Cases	Study[2]
Fraser *et al.,* 1990[30]	34,198	Both	190,000 person-years	14	CSDA
Heath *et al.,* 1997[31]	998,904	Both	7 years	335	CPSII
Nordlund *et al.,* 1997[32]	26,032	Female	600,000 person-years	94	Swedish females
Chow *et al.,* 2000[33]	363,992	Male	5,783,888 person-years	759	Swedish males
Nicodemus *et al.,* 2004[34]	34,637	Female	466,398 person-years	124	IWHS

[1]Superscripts in this column are references.–[2]Studies: CSDA, California Seventh-day Adventists[57]; CPSII, Cancer Prevention Study II[58]; Swedish females, 1963 Swedish Smoking Habits Study[59]; Swedish males, Bygghälsan Occupational Safety and Health among Construction Workers[60]; IWHS, Iowa Women's Health Study.[61]

Smoking categories

Exposure to inhaled tobacco smoke was reported in the abstracted publications using 12 separate categories. The most prevalent model was to divide smokers into categories, 1–9, 10–20 or >20 cigarettes/day. Meta-analyses were carried out using these categories. In addition to these, the 12 reported categories of exposures were condensed to 3 *a priori* groups, termed light, moderate and heavy smokers. The light group was limited to those that smoked 1–9 cigarettes/day or had <25.5 pack-years of exposure. The moderate group contained those who smoked 10–20, <20 or <15 cigarettes/day or who had 25.5–50 pack-years of exposure. Finally, the heavy group contained those that smoked >20, 20–29, ≥25, ≥30, 20–39 or ≥40 cigarettes/day or who had >50 pack-years of exposure. Duration of smoking was reported in the abstracted publications using 8 separate categories that were condensed to 2 *a priori* groups, termed short-term (<25 years) and long-term (≥25 years) smokers. The short-term smoker group contained those who had smoked for 1–24 or <20 years. The long-term smoker group contained those who had smoked for ≥21, ≥25, ≥30 or ≥41 years. Not classified were those who smoked <30, 21–30 or ≥21 years, as these would generate overlap between groups. Length of time since quitting smoking was reported in the abstracted publications using 13 separate categories, and was likewise condensed into 2 *a priori* groups. Short-term ex-smokers contained those who had quit smoking <10 years (reported categories: 1–5, 6–10 or 1–9 years) before diagnosis. Long-term ex-smokers contained those who had quit smoking >10 years (reported categories: >10, 10–14, 10–19, ≥15, 16–25, ≥20 or ≥26 years). Not grouped were those who had quit smoking 1–19 or 6–15 years before diagnosis. The definition of "former smoker" varied between studies. Within the case-control studies, 8 studies did not present data related to former smokers,[5,6,10,14,15,19,26,27] 5 studies did not define the former smoker category,[7,8,17,21,23] 4 studies defined former smokers as those having quit 1 year before diagnosis,[9,11,20,24] one study as 2 years before diagnosis,[25] and one study as 5 years before diagnosis.[16] Within the cohort studies, 2 did not report data related to former smokers,[30,34] 2 did not define former smokers[31,33] and one study defined former smokers as those who had quit smoking 1 year before baseline questionnaire.[32]

Statistical analysis

Meta-analysis was conducted to estimate RR and corresponding 95% CI. The χ^2-test of heterogeneity (denoted as the Q-test), which is based on a weighted sum of the squares of the log odds ratios estimated in the individual studies and the summary log odds ratio, was conducted for each study, as was the Egger's test for publication bias. Independent estimates were generated separately using adjusted or crude RR stratified by year of publication, number of participants, control type, region, smoking status and gender. For overall estimates based on all reported risks, the calculated RR is reported with and without study exclusion. Summary RR were estimated with the statistical program STATA, version 8.0, by inverse-variance weighting, using fixed- and random-effects models that included a term for heterogeneity. All reported summary estimates in this study are based on the random-effects model. Publication bias was assessed using the funnel plot method of Begg and Mazumdar[47] and the regression asymmetry test of Egger *et al.*[48] An influence analysis was carried out for the overall estimate that excluded one study at a time to determine the magnitude of influence on the overall summary estimate. The analysis showed that the overall summary estimate did not change as a result of the exclusion of any one study. Attributable risks were calculated for each study using the method of Breslow and Day.[49]

TABLE III – SUMMARY OF STUDIES USED FOR META-ANALYSIS

Reference	RR	Ever smoker			Former smoker			Current smoker			AR[1] (%)
		Male	Female	Combined	Male	Female	Combined	Male	Female	Combined	
Case-control studies											
5	Crude	4.6 (1.8–12.7)	2.0 (0.4–11.5)	3.8 (1.6–8.9)	—	—	—	—	—	—	64
6	Crude	—	—	2.0 (1.2–3.2)	—	—	—	—	—	—	38
7	Adjusted[2]	—	—	—	—	—	—	1.1 (0.5–2.2)	1.0 (0.3–3.4)	1.0 (0.6–1.9)	−4
	Crude	—	—	—	1.1 (1.8–12.7)	0.7 (0.2–2.8)	—	1.1 (0.4–3.2)	0.9 (0.2–3.2)	1.0 (0.4–2.3)	
8	Adjusted[3]	1.1 (0.7–1.8)	1.0 (0.5–1.9)	1.1 (0.7–1.6)	1.1 (0.6–2.3)	0.7 (0.3–1.8)	1.0 (0.6–1.7)	—	—	—	3
	Crude	1.1 (0.7–1.8)	1.0 (0.5–2.0)	1.0 (0.7–1.5)	1.1 (0.6–2.3)	0.7 (0.2–2.0)	1.0 (0.6–1.7)	—	—	—	
9	Adjusted[4]	—	—	1.2 (0.9–1.6)	—	—	1.4 (0.8–2.2)	—	—	—	3
	Crude	—	—	1.3 (0.9–1.8)	1.3 (0.8–2.3)	1.4 (0.4–4.5)	—	1.6 (1.0–2.8)	0.8 (0.4–1.6)	—	
10	Adjusted	—	—	1.0 (0.5–2.3)	—	—	—	—	—	—	3
	Crude	—	—	1.0 (0.6–1.8)	—	—	—	—	—	—	
11	Adjusted[5]	—	—	1.1 (0.9–1.4)	0.9 (0.7–1.5)	1.1 (0.7–1.7)	—	1.4 (1.0–2.0)	1.0 (0.7–1.6)	—	5
	Crude	—	—	1.1 (0.9–1.4)	1.4 (1.0–2.0)	1.1 (0.7–1.6)	—	0.9 (0.7–1.3)	1.0 (0.6–1.7)	—	
14	Adjusted[6]	1.3 (0.9–1.9)	1.8 (1.0–3.0)	1.4 (1.0–1.9)	—	—	—	—	—	—	—
15	Adjusted[7]	1.6 (1.1–2.4)	1.9 (1.6–3.1)	1.7 (1.3–2.3)	—	—	—	—	—	—	31
	Crude	1.6 (1.0–2.4)	1.8 (1.2–2.7)	1.7 (1.3–2.3)	—	—	—	—	—	—	
16	Adjusted[8]	2.1 (1.1–4.4)	1.1 (0.5–2.4)	1.6 (0.8–2.9)	2.7 (1.0–6.8)	1.4 (0.5–4.3)	—	—	—	—	27
	Crude	1.9 (1.0–3.7)	1.1 (0.4–2.6)	1.6 (0.9–2.6)	2.2 (0.9–5.4)	1.3 (0.4–4.8)	—	2.2 (1.1–4.5)	1.0 (0.4–2.6)	—	
17	Adjusted[9]	—	—	1.3 (1.0–1.7)	—	—	1.1 (0.7–2.4)	—	—	—	−2
	Crude	—	—	1.0 (0.7–1.3)	—	—	1.1 (0.7–1.7)	—	—	0.9 (0.6–1.3)	
19	Adjusted	—	1.3 (0.9–1.9)	—	—	—	—	—	—	—	11
20	Adjusted[10]	2.0 (1.4–2.8)	1.9 (1.3–2.6)	1.9 (1.5–2.5)	—	—	—	—	—	—	38
	Crude	2.0 (1.4–2.9)	1.8 (1.3–2.5)	1.9 (1.5–2.4)	—	—	—	—	—	—	
21	Adjusted[11]	—	—	1.6 (1.2–2.1)	1.6 (0.9–2.9)	1.1 (0.4–2.7)	—	—	—	—	25
	Crude	—	—	1.6 (1.1–2.2)	1.6 (0.9–3.1)	1.3 (0.5–3.6)	—	2.2 (1.2–3.8)	1.0 (0.5–2.1)	—	
23	Adjusted[12]	—	—	1.3 (1.1–1.5)	—	—	1.2 (1.0–1.4)	—	—	1.4 (1.2–1.7)	5
	Crude	—	—	1.2 (1.0–1.3)	—	—	1.0 (0.9–1.2)	—	—	1.3 (1.1–1.5)	
24	Adjusted[13]	1.4 (1.1–1.8)	1.2 (0.9–1.6)	1.4 (1.1–1.6)	1.3 (1.1–1.7)	1.1 (0.8–1.5)	1.2 (1.0–1.5)	1.6 (1.2–2.1)	1.5 (1.0–2.1)	1.5 (1.2–1.9)	18
	Crude	—	—	1.4 (1.2–1.6)	1.4 (1.1–1.7)	1.1 (0.8–1.5)	1.2 (1.0–1.5)	1.7 (1.2–2.2)	1.4 (1.0–2.0)	1.6 (1.3–1.9)	
25	Adjusted[14]	1.8 (1.3–2.7)	1.2 (0.8–1.8)	1.5 (1.0–2.2)	1.7 (1.2–2.6)	0.9 (0.5–1.6)	—	2.1 (1.3–3.2)	1.4 (0.9–2.3)	—	21
	Crude	2.1 (1.4–3.0)	1.3 (0.9–1.9)	1.6 (1.0–2.6)	—	—	—	—	—	—	
26	Adjusted[15]	—	—	2.2 (1.3–3.7)	—	—	—	—	—	—	41
	Crude	—	—	2.5 (1.6–4.1)	—	—	—	—	—	—	—
27	Crude	1.0 (0.6–1.6)	1.5 (1.0–2.3)	—	—	—	—	—	—	—	20
Cohort studies											
30	Adjusted[16]	—	—	2.2 (0.6–8.0)	—	—	—	—	—	—	21
31	Adjusted[7]	—	—	1.5 (1.2–1.9)	1.7 (1.1–2.4)	1.2 (0.7–1.9)	—	1.7 (1.2–2.6)	1.4 (0.9–2.3)	—	26
32	Adjusted[17]	—	1.3 (0.8–2.1)	—	—	1.9 (0.8–4.6)	—	—	1.1 (0.6–2.0)	—	3
33	Adjusted[18]	1.5 (1.2–1.8)	—	—	1.3 (1.0–1.6)	—	—	1.6 (1.3–1.9)	—	—	38
34	Adjusted[7]	—	0.9 (0.6–1.4)	—	—	—	—	—	—	—	—

[1]AR, attributable risk.–[2]Adjusted for age, gender, and date of surgery.–[3]Adjusted for age, gender, ethnic origin, hospital, and date of admission.–[4]Adjusted for age, gender, area of residence, education, and BMI.–[5]Adjusted for age and education.–[6]Adjusted for age, alcohol use, and gender (when appropriate).–[7]Adjusted for age.–[8]Adjusted for age, gender, ethnic origin, and area of residence.–[9]Adjusted for BMI, European ancestry, gender, age, education, income, job, and heart disease.–[10]Adjusted for age and BMI.–[11]Adjusted for age, gender, and year of physical examination.–[12]Adjusted for age, gender, center, and BMI.–[13]Adjusted for education.–[14]Males adjusted for age, total energy, farming, fruits, coffee, and BMI at age 20; females adjusted for age, total energy, education, vegetables, first degree relatives, and BMI at age 40.–[15]Adjusted for age, gender, ethnic origin, education, occupation, and medical conditions.–[16]Adjusted for age and gender.–[17]Adjusted for age and area of residence.–[18]Adjusted for age, BMI, and diastolic blood pressure.

Results

Overall risk associated with cigarette smoking

The studies used for this meta-analysis are outlined in Tables I and II. The RR for RCC associated with cigarette smoking were reported in a variety of ways, including stratification for smoking status and sex. The reported estimates for each study are summarized in Table III. There was tremendous heterogeneity in the methods used to adjust the reported risks (see footnotes in Table III). For ever smoking men, the range of adjusted estimates was between 1.1–2.1, for ever smoking women between 0.9–1.9, and for ever smokers combined between 1.0–2.2. Two of the studies[5,6] shown in Table I did not report estimates associated with cigarette smoking; however, in those studies the number of smoking cases and controls were reported, which allowed for the calculation of the crude RR with corresponding 95% CI. The crude RR for every study for which calculation was possible is also shown in Table III. The study of Bennington and Laubscher[5] reported an RR of 4.6 (95% CI = 1.8–12.7) for male ever smokers. This RR is 2-fold greater than the estimate reported by any other study for ever smokers.

An overall combined estimate was generated for ever smoking cigarettes for both genders combined. As shown in Figure 1, the overall combined RR for the development of RCC associated with ever smoking cigarettes was 1.38 (95% CI = 1.27–1.50) as compared to lifetime never smokers. Risks reported by Muscat *et al.*,[11] Kreiger *et al.*[20] and Nicodemus *et al.*[34] induced heterogeneity into the summary estimate. When these 3 studies were excluded from the analysis to reduce heterogeneity, the RR was essentially unchanged [1.39 (95% CI = 1.30–1.49)], but with a concomitant shift in heterogeneity as measured by the *Q*-test (from $p = 0.083$ to $p = 0.737$).

Attributable risks (AR) from smoking were calculated for 22 of the studies and are shown in Table III. For population-based case-control studies and cohort studies, the median AR was 21% and 23%, respectively. For hospital-based case-control studies, however, the median AR was 3%. This enormous difference in AR for the hospital-based studies is due likely to extreme variations in the proportion of smokers present in the control group.

Gender-specific risks associated with cigarette smoking

The results of meta-analyses carried out using all reported adjusted or crude estimates are shown in Tables IV and V for men and women, respectively. For men, the overall estimate for RCC in ever smokers was 1.50 (95% CI = 1.37–1.65) as compared to those who never smoked. *Q*-tests indicated heterogeneity existed in the summary estimates based on reported adjusted measures. Exclusion of one study[11] from the meta-analysis yielded acceptable tests for heterogeneity and publication bias, but did not affect the estimated RR. In Table IV, note that the summary estimates generated from hospital-based case-control studies were appreciably lower than those from population-based case-control studies. Also note that the estimate generated from prospective cohort studies was in agreement with the overall summary estimate generated from all studies. For women (Table V), the overall RR for RCC in ever smokers was 1.27 (95% CI = 1.14–1.40) as compared to those who never smoked. Exclusion of a single study[20] reduced heterogeneity and yielded a summary estimate of 1.22 (95% CI = 1.09–1.36). As was observed for men, hospital-based case-control studies generated lower estimates as compared to population-based case-control studies. As observed for the estimates in men, the risk estimated by large prospective cohort studies was in agreement with the overall summary estimate generated from all studies.

Meta-analyses for RCC risk stratified by smoking status and gender were conducted using reported adjusted RR (Table VI) and crude RR (Table VII). The RR is reduced in former smokers as compared to current smokers for each category. Interestingly, the risks for ever smokers typically were closer to those for current smokers, indicating that perhaps most ever smokers are current smokers or that few cases were long-term former smokers.

Dose-dependent RR and effect of quitting smoking

For men and women, a dose-dependent increase in risk was observed concomitant with the number of cigarettes smoked per day (Table VIII). Given the wide array of measurement categories reported in the literature, dose/risk relationships were assessed for those that smoked ½, 1 or >1 pack of cigarettes/day. The RR increased from 1.60 (95% CI = 1.21–2.12) in male smokers who smoked 1–9 cigarettes/day to 2.03 (95% CI = 1.51–2.74) in those that smoked >20 cigarettes/day. Likewise the estimate in women rose from 0.98 (95% CI = 0.71–1.35) to 1.58 (95% CI = 1.14–2.20) with increasing numbers of cigarettes smoked per day. To condense the varying reported categories, smokers were divided into 3 groups (light, moderate and heavy smoker) as described in the Subjects and Methods section. Again, for men and women there was an increase in RR associated with heavier doses to inhaled tobacco smoke. The effects seen for duration of smoking (short-term smoker *vs.*

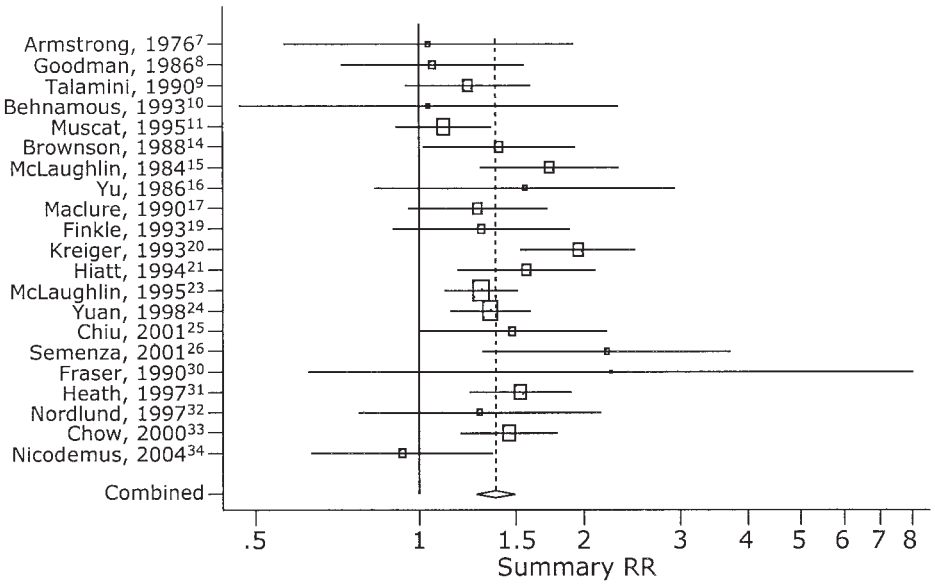

FIGURE 1 – A Forrest plot for estimated RR is shown for all studies reporting adjusted RR for ever smokers. For each study, the reference number is included. *Q*-test for heterogeneity ($p = 0.083$).

TABLE IV – META-ANALYSIS OF RISK FOR RCC FROM TOBACCO SMOKING IN MEN

Variable	Estimates	Adjusted RR	Adjusted 95% CI	Test for heterogeneity[1]	Egger's test[2]	Estimates	Unadjusted RR	Unadjusted 95% CI	Test for heterogeneity	Egger's test
Overall										
All estimates	20	1.50	1.37–1.65	0.237	0.992	22	1.58	1.38–1.82	0.009	0.275
Estimates excluded	18[3]	1.54	1.42–1.68	0.563	0.515	20[4]	1.52	1.35–1.70	0.614	0.547
Year of publication										
1968–1990	7	1.40	1.14–1.70	0.471	0.962	11	1.54	1.26–1.88	0.413	0.511
1991–2004	13	1.53	1.38–1.70	0.157	0.770	11	1.60	1.32–1.94	0.001	0.312
Participants										
<100 cases	6	1.59	1.28–1.97	0.611	0.310	8	1.63	1.22–2.19	0.336	0.389
≥100–499 cases	12	1.53	1.35–1.73	0.091	0.940	13	1.60	1.34–1.92	0.003	0.601
≥500–999 cases	1	1.34	1.05–1.70	—	—	1	1.37	1.08–1.73	—	—
≥1000 cases	1	1.30	0.90–1.89	—	—	—	—	—	—	—
<35,000 in cohort	—	—	—	—	—	—	—	—	—	—
≥35,000 in cohort	4	1.52	1.34–1.73	0.454	0.948	—	—	—	—	—
Control type										
Hospital	6	1.17	0.98–1.40	0.644	0.496	9	1.29	1.02–1.63	0.137	0.287
Population	10	1.66	1.47–1.86	0.637	0.011	13	1.75	1.51–2.02	0.124	0.073
Individual matched	8	1.43	1.23–1.66	0.539	0.899	14	1.54	1.34–1.75	0.455	0.280
Frequency matched	8	1.54	1.28–1.86	0.056	0.879	7	1.68	1.28–2.21	0.001	0.036
Region										
Europe	3	1.45	1.26–1.68	0.272	0.480	4	1.40	0.99–1.97	0.855	0.318
North America	17	1.53	1.37–1.70	0.214	0.374	18	1.62	1.38–1.90	0.002	0.250

[1]*p*-value for *Q*-test for heterogeneity ($p < 0.05$ indicates potential heterogeneity).–[2]*p*-value for Egger's test for bias ($p < 0.05$ indicates potential publication bias).–[3]Excluded estimates from reference 11.–[4]Excluded estimates from references 5,11,25.

TABLE V – META-ANALYSIS OF RISK FOR RCC FROM TOBACCO SMOKING IN WOMEN

	Estimates	Adjusted RR	Adjusted 95% CI	Test for heterogeneity[1]	Egger's test[2]	Estimates	Unadjusted RR	Unadjusted 95% CI	Test for heterogeneity	Egger's test
Overall										
All Estimates	22	1.27	1.14–1.40	0.460	0.587	22	1.29	1.15–1.45	0.684	0.101
Estimates excluded	21[3]	1.22	1.09–1.36	0.765	0.865	—	—	—	—	—
Year of publication										
1968–1990	7	1.40	1.07–1.82	0.376	0.043	11	1.24	0.96–1.58	0.610	0.004
1991–2004	15	1.24	1.10–1.39	0.475	0.502	11	1.30	1.14–1.48	0.521	0.318
Participants										
<100 cases	9	1.20	0.94–1.52	0.934	0.336	12	1.01	0.77–1.33	0.994	0.497
≥100–499 cases	11	1.26	1.08–1.47	0.101	0.624	10	1.35	1.17–1.56	0.270	0.469
≥500–999 cases	—	—	—	—	—	—	—	—	—	—
≥1000 cases	2	1.43	0.88–2.33	0.232	—	—	—	—	—	—
<35,000 in cohort	3	1.05	0.77–1.42	0.387	0.195	—	—	—	—	—
≥35,000 in cohort	2	1.30	0.93–1.83	0.659	—	—	—	—	—	—
Control type										
Hospital	6	1.12	0.89–1.41	0.526	0.806	9	1.00	0.78–1.28	0.971	0.251
Population	11	1.36	1.18–1.57	0.367	0.810	12	1.40	1.22–1.60	0.598	0.715
Individual matched	9	1.19	1.00–1.42	0.896	0.594	14	1.13	0.95–1.36	0.963	0.219
Frequency matched	8	1.37	1.11–1.68	0.097	0.292	7	1.37	1.13–1.67	0.191	0.072
Region										
Europe	3	1.24	0.78–1.98	0.591	0.659	4	0.88	0.52–1.48	0.819	0.557
North America	19	1.26	1.13–1.42	0.337	0.590	18	1.31	1.17–1.48	0.642	0.210

[1]*p*-value for *Q*-test for heterogeneity ($p < 0.05$ indicates potential heterogeneity).–[2]*p*-value for Egger's test for bias ($p < 0.05$ indicates potential publication bias).–[3]Excluded estimates from reference 20.

long-term smoker) were not as great, although these estimates were based on fewer studies. The protective value of smoking cessation was notable in the studies restricted to men, but was not observed in women. Note that there was considerable heterogeneity in the estimates for men, however, which required the exclusion of the estimates in 2 studies[11,22] to obtain appropriate RR.

Discussion

Suspected risk factors for RCC have been evaluated through numerous case-control and cohort studies; however, all of the evaluated factors (cigarette smoking, obesity, high intake of dairy products and low consumption of fruits and vegetables, lack of physical activity, low socioeconomic status, hypertension, treatment of hypertension with thiazide diuretics, family history of disease and multiparity) have modest effects.[50] Of these potential risk factors, perhaps cigarette smoking is the most intriguing. Those that have supported previously a causal relationship between smoking and the formation of RCC have noted the clear dose-response correlation and the observed benefit of smoking cessation on risk.[50–52] This meta-analysis confirms the dose-dependence of increasing RR with increased exposure to cigarette smoke. Our data suggest the risk for light to moderate smokers is greater than previously estimated.[51] Likewise, a drop in RR was noted for long-term former smokers as compared to short-term cessation, although it should be noted that there was tremendous heterogeneity in the methods used to determine the length of smoking cessation in the evaluated studies. It is possible that there is even a greater benefit

TABLE VI – META-ANALYSIS USING REPORTED RR BY SMOKING STATUS

Gender	Ever smokers		Former smokers		Current smokers	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Cohort studies						
Combined	1.55	1.25–1.91	—	—	—	—
Male	1.46[1]	1.19–1.79	1.42	1.11–1.81	1.62	1.36–1.92
Female	1.05	0.77–1.42	1.33	0.86–2.06	1.28	0.88–1.85
Population-based case-control studies						
Combined	1.39	1.17–1.64	1.21	1.07–1.37	1.45	1.26–1.66
Male	1.83	1.50–2.24	1.48	1.23–1.80	1.72	1.33–2.22
Female	1.51	1.21–1.88	1.05	0.81–1.37	1.44	1.09–1.90
Hospital-based case-control studies						
Combined	1.24	0.95–1.63	1.16	0.80–1.67	—	—
Male	1.22	0.91–1.65	0.95	0.68–1.32	1.33	0.98–1.80
Female	1.37	0.77–2.43	1.02	0.68–1.52	1.00	0.68–1.48
All studies combined						
Combined	1.34	1.20–1.51	1.21	1.07–1.36	1.45	1.26–1.66
Male	1.61	1.34–1.93	1.37	1.17–1.61	1.59	1.40–1.80
Female	1.37	1.11–1.70	1.09	0.90–1.33	1.27	1.05–1.55

[1]This estimate based on a single study.

TABLE VII – META-ANALYSIS USING CRUDE RR BY SMOKING STATUS

Gender	Ever smokers		Former smokers		Current smokers	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Population-based case-control studies						
Combined	1.43	1.08–1.89	1.12	0.98–1.27	1.28	1.01–1.64
Male	1.68	1.31–2.15	1.48	1.23–1.79	2.12	1.57–2.84
Female	1.56	1.30–1.88	1.06	0.81–1.40	1.44	1.11–1.88
Hospital-based case-control studies						
Combined	1.28	0.85–1.93	0.97[1]	0.56–1.67	—	—
Male	2.11	0.51–8.64	1.33	1.03–1.73	1.15	0.77–1.72
Female	1.10	0.58–2.06	1.01	0.70–1.46	0.95	0.64–1.40
All studies combined						
Combined	1.37	1.11–1.68	1.11	0.99–1.24	1.28	1.01–1.64
Male	1.67	1.27–2.20	1.43	1.23–1.66	1.70	1.21–2.39
Female	1.52	1.27–1.82	1.04	0.84–1.30	1.25	1.01–1.53

[1]This estimate based on a single study.

TABLE VIII – DOSE, DURATION, AND LENGTH OF QUITTING EFFECTS OF CIGARETTE SMOKING

	Estimates	Adjusted		Test for heterogencity[1]	Egger's test[2]	Estimates	Unadjusted		Test for heterogencity	Egger's test
		RR	95% CI				RR	95% CI		
Male										
1–9 cigarettes/day	4	1.60	1.21–2.12	0.899	0.308	4	1.51	1.15–1.99	0.761	0.275
10–20 cigarettes/day	3	1.83	1.30–2.57	0.990	0.652	3	1.85	1.35–2.54	0.996	0.276
>20 cigarettes/day	5	2.03	1.51–2.74	0.759	0.480	5	1.91	1.51–2.43	0.623	0.872
Light smoker	5	1.48	1.16–1.88	0.794	0.491	5	1.44	1.14–1.82	0.789	0.394
Moderate smoker	8	1.52	1.23–1.88	0.697	0.718	10	1.52	1.29–1.79	0.466	0.712
Heavy smoker	13	1.76	1.52–2.04	0.815	0.110	17	1.78	1.58–2.02	0.669	0.196
Short-term smoker	2	1.12	0.73–1.70	0.679	—	2	1.16	0.78–1.72	0.454	—
Long-term smoker	3	1.28	1.10–1.48	0.384	0.418	3	1.36	1.82–2.26	0.040	0.100
Short-term ex-smoker	5	1.75	1.41–2.18	0.866	0.110	5	1.85	1.49–2.31	0.904	0.211
Long-term ex-smoker	5	1.21	0.86–1.70	0.001	0.319	5	1.22	0.90–1.73	0.004	0.479
Studies excluded[3]	2	1.24	0.99–1.55	0.728	—	2	1.24	0.99–1.54	0.785	—
Female										
1–9 cigarettes/day	4	0.98	0.71–1.35	0.949	0.434	4	1.06	0.77–1.44	0.945	0.655
10–20 cigarettes/day	3	1.38	0.90–2.11	0.843	0.494	3	1.75	1.22–2.50	0.379	0.057
>20 cigarettes/day	4	1.58	1.14–2.20	0.849	0.877	4	1.60	1.15–2.23	0.765	0.669
Light smoker	5	1.09	0.82–1.46	0.576	0.346	5	1.18	0.90–1.54	0.678	0.669
Moderate smoker	7	1.32	1.04–1.68	0.734	0.678	9	1.41	1.11–1.80	0.264	0.081
Heavy smoker	12	1.50	1.19–1.88	0.374	0.810	15	1.48	1.22–1.80	0.476	0.828
Short-term smoker	2	1.06	0.56–2.00	0.885	—	2	1.17	0.62–2.18	0.708	—
Long-term smoker	2	1.18	0.97–1.44	0.632	—	2	1.28	0.85–1.92	0.379	—
Short-term ex-smoker	5	1.07	0.79–1.46	0.722	0.085	5	1.08	0.79–1.48	0.824	0.107
Long-term ex-smoker	5	1.27	0.97–1.66	0.835	0.038	5	1.22	0.94–1.59	0.826	0.035

[1]*p*-value for *Q*-test for heterogencity ($p < 0.05$ indicates potential heterogencity).–[2]*p*-value for Egger's test for bias ($p < 0.05$ indicates potential publication bias).–[3]Excluded estimates from references 11,20.

of long-term smoking cessation on the risk of developing RCC, but the heterogeneity in the methods used to report this effect precluded calculation of this estimate.

There was a conspicuous difference in the RR calculated from hospital-based case-control studies as opposed to population-based case-control studies and cohort studies. This meta-analysis seems to support the concerns often expressed about such studies with respect to the over-representation of smokers in control groups.[53] Each of the published studies addressed specifically this concern by eliminating patients with diseases known to be associated with cigarette smoking. The RR obtained from the meta-analysis in hospital-based studies was 1.17 (95% CI = 1.03–1.33) as opposed to the RR from population-based studies, which was 1.49 (95% CI = 1.34–1.66). These summary estimates were significantly different from one another ($p = 0.003$, Q-test for heterogeneity). The summary estimate for population-based case-control studies is comparable to the estimate calculated from the cohort studies, which was 1.42 (95% CI = 1.24–1.61). The summary estimate for cohort studies was not different from the estimate generated from population-based studies ($p = 0.853$), but was different statistically from the summary estimate generated from hospital-based studies ($p = 0.032$). Therefore, it seems that either the list of diseases known to be related to cigarette smoking is inadequate, perhaps because some diseases that are not classified currently as being related to cigarettes smoking are in fact related to smoking, or that smokers are over-represented in hospital-based controls because smokers are more prone to most diseases or to hospitalization. At any rate, estimates of smoking risk from hospital-based studies should be viewed with increased awareness of the potential for under-estimation.

Another concern for the stability of the meta-analysis estimates was centered on differential survival associated with smoking in patients with RCC. Data indicate that in those cases with RCC, current smokers are at increased risk of death as compared to non-smokers (hazard ratio [HR] 1.7, 95% CI = 1.2–2.5).[54] This association is stronger within six months of diagnosis (HR = 2.5, 95% CI = 1.5–4.3). The association was explained by the increased stage at diagnosis for current smokers, who were more likely to have distant metastases at the time of diagnosis. It is possible that case-control studies may be biased if cases who do not participate owing to shorter survival have different smoking histories than those who do participate. This concern seems to be supported by another study that found that even in those cases without distant metastases, smokers had a significantly worse overall survival rate than did non-smokers.[55] Paradoxically, we found that risk estimates reported in hospital-based studies, in which rapid case assessment is more likely, were consistently lower than those reported in population-based studies in which rapid case assessment may not be possible. In this meta-analysis, the survival bias (mainly affecting population-based case-control studies) is likely offset by selection bias (mainly affecting hospital-based case-control studies).

We observed a large RR in male smokers as compared to female smokers, even when comparable doses were considered. This discrepancy may be related to a true increased risk in men, but also could be explained by the maturity of the smoking trends in the studied populations. For example, in the United Kingdom, smoking prevalence at ages 25–34 were 80% for men and 53% for women in 1948–1952.[56] A simple comparison of ever *vs.* never smokers or by cigarettes consumed per day, therefore, would likely result in a longer exposure duration for the greater proportion of men as compared to women. We consistently observed a greater summary estimate for risk when these measures were assessed in this meta-analysis. A more rigorous analysis that considers dose and duration of exposure (*e.g.*, pack-years of exposure) was not possible given that the majority of reports either did not report risk by pack-years of exposure or did not categorize by gender when exposure by pack-years was reported. Krieger *et al.*[20] reported risks for men and women who had smoked <1 or >1 pack of cigarettes/day for 20 or more years. They observed RR of 2.2 (95% CI = 1.4–3.5) for men and 1.7 (95% CI = 1.1–2.7) for women who smoked less than 1 pack per day. For those who smoked greater than 1 pack per day, the RR were identical: 2.2 (95% CI = 1.5–3.3) and 2.2 (95% CI = 1.4–3.4) for men and women, respectively.

To limit the potential for publication bias in this meta-analysis, we were careful to collect as many studies as possible related to risk and RCC and specifically went to great effort to obtain publications that focused on risk factors other than smoking. In many instances, studies that failed to list smoking or tobacco in the title nevertheless reported non-significant risks for cigarette smoking. The potential for publication bias was further exacerbated by our desire to obtain summary estimates for dose effects, as it seemed probable that studies that failed to observe an overall association with cigarette smoking would be less likely to report dose-specific rates. Of the 21 case-control studies used for the meta-analysis, 18 reported OR stratified by dose (none of the cohort studies reported dose relationships). For the 11 studies that reported a statistically significant association with smoking, all 11 reported dose information.[5,6,11,14–16,20,23–26] For the 6 studies that failed to observe a significant association, 4 reported dose information.[7–10] Two studies did not report an overall risk estimate for smoking.[17,27] Interestingly, one of these studies[17] did report cigarette dose information that was used to calculate a crude OR for the meta-analysis. Of the studies that specifically addressed tobacco as an *a priori* risk, 7 of 7 reported dose information for cigarette smoking.[5,14,16,23–26] Of the 5 studies that focused on other risk factors for RCC (coffee and animal protein consumption, diet, diuretic use and physical activity), only 2 reported cigarette dose information.[7,17] Even though the Egger's test for publication bias was negative for all dose estimates, based on this assessment, it seems likely that there is a slight over-estimation of the effects of cigarette dose in the reported summary estimates (Table VIII). There is, however, clearly a dose-dependent increase in risk with increasing cigarette consumption.

Based on this meta-analysis compiled from 26 studies spanning 37 years, it is clear that cigarette smoking exerts a modest, but significant increase in the risk for one developing RCC. The overall risk of RCC seems to be stronger in men than in women, but when numbers of cigarettes smoked per day is considered, the risks are approximately the same for a given dose. Likewise, the advantages of smoking cessation were observed in reduced risk for both genders.

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