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Parity and risk of lung cancer in women: Systematic review and meta-analysis of epidemiological studies

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ABSTRACT

Multiple studies have assessed parity as a risk factor for lung cancer but results have been inconclusive. We searched MEDLINE (through August 2010) and the Institute of Scientific Information Web of Knowledge database (through April 2011) to identify studies investigating the association of parity with lung cancer and allowing the calculation of dose–response trends using a linear model. Between-study heterogeneity was assessed using Cochran's *Q* statistic and the *I*² index. Summary per-child relative risks (RRs) with their 95% confidence interval (CI) were estimated using random effects meta-analysis. Sixteen eligible studies (8077 lung cancer patients; 350,295 unaffected individuals) provided data for meta-analysis. There was significant between-study heterogeneity ($p < 0.001$; $I^2 = 73\%$). The summary per livebirth RR was 0.98 (95% CI, 0.95–1.02), indicating no effect of parity on lung cancer risk. Results were consistent in case–control ($n = 11$), RR = 0.99 (95% CI, 0.94–1.04), and cohort studies ($n = 5$), RR = 0.97 (95% CI, 0.92–1.03). Studies not including small-cell lung cancer patients found a borderline protective effect of parity, RR = 0.94 (95% CI, 0.88–1.00). In contrast, no effect was observed in studies including small-cell lung cancer patients, RR = 1.00 (95% CI, 0.98–1.03); p for difference = 0.05. Overall, there was little evidence of a dose–response relationship between increasing number of livebirths and lung cancer; however, studies have produced heterogeneous results. Future studies should include analyses in well-defined histological disease subgroups.

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1. Introduction

In 2010 more than 100,000 women were diagnosed with lung cancer in the USA; the disease is the most frequent cause of cancer-related death among women in the USA and the second most frequent cause world-wide [1,2]. Although lung cancer mortality among men has reached a plateau or is declining in most countries, it continues to increase among women in developing countries [3,4]. The identification of environmental exposures predisposing to the development of lung cancer, such as tobacco consumption, environmental tobacco smoke and asbestos, are among the greatest successes of epidemiology and explain the bulk of the population

incidence of lung cancer [5–7]. Yet, lung cancer arises in never smokers and a complex interplay of genetic and hormonal factors is believed to modify the effect of environmental carcinogens on disease initiation and progression [7].

It has been hypothesized that women may be more susceptible to the carcinogenic effects of tobacco and that lung cancer in women may be biologically and clinically different from disease in men [8,9]. Case–control studies in the 1990s suggested that, for the same amount of tobacco exposure, women may be at increased risk for lung cancer compared to men [10]. Several large cohort studies failed to confirm this association and the issue remains controversial [11–15]. Regardless of whether women have an increased susceptibility to the carcinogenic effects of smoking, lung cancer in women appears to have a different natural history compared to men, with several studies demonstrating superior survival for women when adjusting for disease stage, histology and treatment [9]. Women are also more likely to develop adenocarcinoma, a histological subtype with weaker associations with tobacco smoking [16]. Additional evidence suggesting that sex-related factors contribute to lung cancer carcinogenesis comes from studies

Abbreviations: CI, confidence interval; IQR, inter-quartile range; ISI, Institute of Scientific Information; MOOSE, Meta-analysis of Observational Studies in Epidemiology; NSCLC, non-small cell lung cancer; RR, relative risk; STROBE, STrengthening the Reporting of OBServational studies in Epidemiology.

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demonstrating a familial aggregation of cancers of the reproductive system among relatives of female lung cancer patients [17,18] as well as the increased lung cancer risk among female survivors of reproductive organ cancers [19–22]. In addition, lung tissue, both non-cancerous and tumor-derived, appears to express hormonal receptors suggesting that it may be responsive to hormonal stimuli [23–26].

Taken together, these observations suggest that hormonal factors may influence lung cancer pathogenesis and have motivated epidemiological studies investigating the association of hormonal and endocrine factors with lung cancer. Among the different exposures that have been investigated, parity (the number of livebirths in a woman's lifetime), is likely less prone to recall bias and misclassification, and – in recent analyses – has been found to be inversely associated with lung cancer risk [27–29]. Many of the studies investigating the parity–lung cancer association are underpowered to detect moderate effect sizes and contradictory results have been reported, ranging from strongly protective effects [27,28] to substantial increases in the risk of the disease with increasing parity [30]. To further investigate the association between parity and lung cancer risk and to identify potential sources of between-study heterogeneity we conducted a systematic review and dose–response meta-analysis of the relevant studies.

2. Methods

2.1. Literature search and eligibility criteria

We searched the MEDLINE database (through Pubmed, from inception to August 31, 2010) to identify studies reporting on epidemiological investigations of the association between parity (defined as the total number of live-births) and lung cancer occurrence.

We used combinations of key words related to the exposure (such as “parity”, “pregnancy”, “livebirth”) and the outcome of interest (“lung cancer”, “pulmonary neoplasm”, “lung adenocarcinoma”), along with a combination of search filters for identifying observational studies. The complete search strategy is available upon request from the authors. We also perused the reference lists of eligible studies and relevant review articles. To increase the yield of our search we used the Institute of Scientific Information (ISI) Web of Knowledge database (last search: April 3, 2011) to identify articles citing the studies we considered eligible. We screened the titles and abstracts of the articles citing the originally identified studies to identify additional potentially eligible articles.

Eligible studies had to have an analytic design (case–control, nested case–control, or cohort) and report or allow the calculation of relative risk (RR) estimates (odds ratios, risk ratios, incidence rate ratios or hazard ratios) with their variance across at least three categories of parity, so as to allow estimation of the dose–response relationship between parity and lung cancer occurrence risk (i.e. studies of lung cancer incidence) [31,32]. Alternatively, we considered studies that directly reported per-child risk estimates and their variance. We only considered studies reporting on at least 20 cases and excluded case reports, case series, comparative studies not using an analytical epidemiologic design, or studies not reporting analyses of primary data (e.g., letters, editorials, narrative reviews). We only considered English-language full text publications. Studies reporting on aero-digestive malignancies other than lung cancer were excluded unless they provided or allowed the calculation of risk estimates separately for lung cancer. We also excluded studies reporting exclusively on lung cancer mortality. When multiple studies pertained to the same or partially overlapping populations, we only considered the report with the longest

follow-up (for cohort studies) or the largest number of cases (for case–control studies) from which data were extractable.

2.2. Data extraction

For each eligible study, two reviewers (IJD and JKP) independently extracted the following information: author, year of publication, population studied (selection of cases and controls for case–control studies; cohort selection and follow-up methods for cohort studies), settings and location where the study was conducted, relevant dates (including periods of recruitment, exposure, follow-up, and data collection), demographics of participants, outcome and exposure definitions (including lung cancer diagnosis and exposure ascertainment methods), use of matching (and variables used for matching cases and controls), number of cases and controls (for case–control studies) or affected and unaffected individuals (for cohort studies) stratified by parity levels, distribution of different lung cancer histologies in affected individuals, smoking related information, the percentage of women receiving hormone replacement therapy, the duration of follow-up, adjusted and unadjusted (when available) RR estimates (comparing participant groups defined by parity) and their variance (or sufficient statistics to calculate that variance). For all comparisons, the primary analysis used the maximally adjusted RR estimates reported from each study. For all descriptive variables we attempted to capture values separately for cases and controls (unaffected individuals); when such information was not available we recorded information for the overall study population.

2.3. Assessment of validity

We considered the following characteristics as being reflective of study validity: definition and measurement of exposure, definition and ascertainment of outcome, participation rates and potential for selection bias, consideration of potential confounders and effect modifiers (such as age and smoking status), methods used to define parity levels (when multiple exposure groups are analyzed), factors used for adjusting RR estimates (with particular focus on the handling of tobacco use-related information, given the strong association with tobacco use and lung cancer development). Regarding model building, we assessed whether a description of the procedure to select the model was provided (i.e., whether any model selection process was described), whether matching variables were entered in the final model (for matched studies). These items are largely consistent with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [33,34]. We did not merge these items into a quality score because different scoring methods produce inconsistent results and may introduce bias [35].

2.4. Evidence synthesis

To estimate summary dose–response coefficients (i.e., per live-birth RRs) from each study we used the methods proposed by Greenland et al. [31,32]. Briefly, for studies that reported RR estimates for at least three exposure categories, we used the log-RRs and their variances along with the marginal data for each exposure category (i.e. the number of cases and the number of controls for case–control studies or the number of cases and total person time for cohort studies) to estimate study-specific per-child RR for lung cancer. For each study, we used the group with the lowest number of livebirths as the reference group [31,32]. For studies not using the category with the lowest number of livebirths as the reference, we used the effective count method proposed by Hamling et al. to recalculate the RR using the stratum with the lowest number of

livebirths as the reference [36]. We assessed graphically whether linearity of the log-RR over parity was a plausible assumption.

Between-study heterogeneity of the per-child RR, estimated from each study was assessed with Cochran's Q statistic and between-study inconsistency was quantified by the I^2 statistic [37,38]. Because of the low power of the Q statistic, we used $p < 0.1$ as the threshold for statistical significance.

We summarized the coefficients across studies using an inverse-variance random effect model [39].

2.5. Sensitivity analyses and assessment of bias

It was expected that for some exposure groups open-ended definitions of parity would be provided [40]. For our primary analysis these categories were assigned a value that was equal to their lower limit plus half the width of the adjacent category. To assess whether our results were sensitive to the method of assigning values to open-ended exposure categories, we performed sensitivity analysis using two alternative approaches by assigning to these categories: (a) the value of their lower limit and (b) a value equal to their lower limit plus the width of the adjacent interval. We also explored the effect of excluding open-ended categories on the meta-analysis results. For each sensitivity analysis we re-calculated the dose-response coefficient from each study and then performed random effects meta-analysis across all studies, as described above.

In additional sensitivity analyses, we explored whether a single study influenced the results of the meta-analysis by calculating the summary RR after excluding each of the eligible studies in turn [41]. We also repeated the analysis using a fixed effects model [41,42].

2.6. Subgroup analyses and assessment of small study effects

To explore potential sources of heterogeneity we assessed the following predefined subgroups: study design, participant ethnicity, completeness of histological confirmation, lung cancer histology, specification of parity modeling details, and whether adjustment for important covariates was performed. To estimate the effect of these study-level covariates on the association of parity with lung cancer, we used random effects meta-regression [43,44].

To explore whether less precise studies reported results that were systematically different from those of more precise studies, we used the egger regression-based test. This test is often referred to as a test for "publication bias" [45,46].

Statistical analyses were conducted using Stata version 11.1/SE (Stata Corp., College Station, TX). Statistical significance was defined as a two-sided p -value < 0.05 for all tests, except those for heterogeneity. Where applicable, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [47].

3. Results

3.1. Eligible studies

Our literature search retrieved 4526 citations of which, after screening of abstracts and titles, 55 were considered potentially eligible and were reviewed in full text. Of these studies, 39 were excluded (Fig. 1) and 16 studies (11 case-control and 5 cohort studies) were considered eligible for inclusion in the meta-analysis. The ISI search retrieved 402 articles citing these 16 studies. After screening titles and abstracts, 35 were considered potentially eligible and were reviewed in full text; however, no additional eligible studies were identified. The characteristics of eligible studies are summarized in Table 1; additional details are presented in Supplementary Table 1.

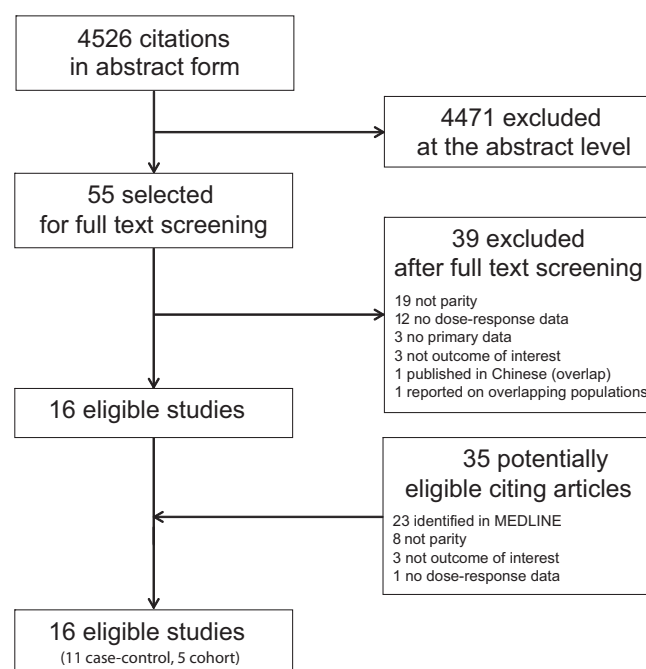


Fig. 1. Search strategy flow.

Eligible studies had been published between 1990 and 2010, and their enrollment periods ranged from 1980 to 2010. Six studies enrolled predominantly (>80%) white individuals, seven enrolled predominantly East Asian populations and two enrolled mixed populations (one study did not report information on the ethnic distribution of participants). Eleven studies had a case-control design (4927 cases and 6443 controls total) and 5 had a cohort design (3150 cases and 343,852 unaffected individuals total), for a combined sample size of 8077 lung cancer patients and 350,295 controls/unaffected individuals. The median number of lung cancer cases was 358 (inter-quartile range, IQR, 171–781) and the median number of controls/unaffected participants was 806 (IQR, 492–39127).

In the 11 case-control studies mean or median participant age ranged between 56 and 66 years for cases and between 55 and 65 years for controls. In the 3 out of 5 cohort studies that provided relevant information, mean or median age of participants at cohort inception ranged between 49 and 63 years. Lung cancer histology information was reported in 15 of the 16 studies and was available for at least 80% of cancer cases in 10 of them. The proportion of adenocarcinoma histology ranged between 3% and 100%, while the proportion of squamous cell histology ranged between 0 and 37%. Of the 15 studies that provided relevant information, 7 studies reported enrolling at least some patients with small-cell lung cancer and 8 studies did not (of those, two studies enrolled only cases with adenocarcinoma histology). In 15 out of 16 studies that provided relevant information the percentage of ever smokers ranged from 0 to 88% and the proportion of never smokers ranged between 8% and 100% among cases (one study did not report data on tobacco consumption and smoking history information).

3.2. Assessment of validity

Our assessment of study validity is summarized in Supplementary Table 2. Most studies used standardized questionnaires and in-person interviews to assess parity and smoking status. Participation rates were reported in 10 of the studies and ranged between 25% and 97%. Seven of these studies had participation rates higher than 80%. The majority of case-control studies

Table 1
Characteristics of eligible studies.^a

Author, year (Country)	Study design Recruitment period	Age in years ^b Menopausal status (premenopausal n, %) Hormone replacement therapy (n, %)	Participants and (cases/controls, unless otherwise stated) follow-up information	Lung cancer histology N (%)
Wu-Williams, 1990 (China) (58)	Case–control 1985–1987	56 [NR]; 55 [NR]	964/959 (of whom 956 cases and 951 of controls had information on parity)	Available for 688 of cases; adenocarcinoma 310 (45); squamous-cell 201 (29); small-cell 117 (17); other 66 (10)
Taioli, 1994 ^c (USA) (59)	Case–control NR	NR	180/303	Adenocarcinoma 180 (100)
Zhou, 2000 (China) (60)	Case–control Cases, 1991–1995; controls, 1988–1989	Cases, 57 [NR]; controls, 57 [NR]	72/72	Adenocarcinoma 72 (100)
Seow, 2002 (Singapore) (61)	Case–control 1996–1998	Cases, 65 [12]; controls, 63 [13]	303/763	Adenocarcinoma 166 (55); squamous-cell 56 (19); small-cell 21 (7); other 60 (20)
Brenner, 2003 (China) (62)	Case–control 1994–1998	Cases: <45, 21 (19); 45–54, 38 (35); 55–64, 34 (31); >65, 16 (15); controls: <45, 51 (12); 45–54, 162 (37); 55–64, 144 (33); >65, 78 (18)	109/435 (of whom 108 cases and 431 controls had information on parity)	Available for 38 of 109 cases; small-cell 16 (42); squamous-cell 14 (37); adenocarcinoma 1 (3); not specified 7 (18)
Kreuzer, 2003 (Germany) (63)	Case–control 1990–1996	Cases, 60 [NR]; controls, 59 [NR]	811/912	Small-cell 207 (26); squamous -cell 174 (22); adenocarcinoma 386 (48); other 44 (5)
Liu, 2005 (Japan) (64)	Prospective cohort (JPHC Study) 1990–1994	Total cohort, 40–49 years 17,915 (40); 50–59 years 18,318 (41); 60–69 years 8444 (19) ^d	Total cohort, n = 44, 677; total person-years = 395, 448 years; incident cases, 153	Adenocarcinoma 118 (77); other 20 (13); unknown 17 (11)
Elliot, 2006 (UK) (30)	Case–control (nested within the RCGP OCS)	Mean age at recruitment in the cohort was 29 years.	162/486	NR
Kabat, 2007 ^e (Canada) (65)	Prospective cohort (NBSS) 1980–1985	Cases, 51 [5]; non-cases 49 [6]	Cases, 750; non-cases, 89,062; mean follow-up = 16.1	Squamous-cell 100 (13); adenocarcinoma 355 (47); small-cell 122 (16); large-cell, 49 (7); other/mixed, 102 (14)
Schwartz, 2007 (USA) (66)	Case–control 2001–2005	Cases, 60 [9]; controls, 58 [9]	488/498	Adenocarcinoma 346 (71); squamous-cell 39 (8); large-cell 15 (3); other 83 (17)
Weiss, 2008 (China) (67)	Prospective cohort (SWHS) 1996–2000	Cases ^f , 19 (9%) 40–44–y; 30 (14%) 45–49 years 25 (11%) 50–54 years; 30 (14%) 55–59 years; 45 (20%) 60–64 years; 71 (32%) ≥65 years. Total person-time, ^g 29% 40–44 years; 21% 45–49 years; 14% 50–54 years; 10% 55–59 years; 13% 60–64 years; 13% ≥65 years	Cases, 220; non-cases, 71,094; 506, 522 total person-years; mean follow-up for cases = 4.1 years	Available for 168 (76) of cases: adenocarcinoma, 78 (46)
Koushik, 2009 (Canada) (68)	Case–control 1996–1997	Cases, 62 [9]; controls, 62 [9]	422/577 (of whom 413 cases and 568 controls had information on parity)	Adenocarcinoma, 201 (48); squamous-cell, 83 (20); small cell, 73 (17); large cell, 37 (9); other, 28 (7)
Seow, 2009 (Singapore) (27)	Prospective cohort (SCHS) 1993–1998	Entire cohort at recruitment, 56 [8]	Cases, 298; non-cases, 33,730; mean follow-up = 9.6 years	Available for 85% of cases: Adenocarcinoma 138 (46)

Table 1

Table 1 (Continued)

Author, year (Country)	Study design Recruitment period	Age in years ^b Menopausal status (premenopausal <i>n</i> , %) Hormone replacement therapy (<i>n</i> , %)	Participants and follow-up information	Lung cancer histology <i>N</i> (%)
Baik, 2010 (USA) (29)	Prospective cohort (NuHS) 1984–2006	63 [38–87] ^h	Cases, 1729; total cohort <i>n</i> = 107, 171 women with 1,590,432 total person-years; follow-up = 22 years	Histologic confirmation for 1505 cases: adenocarcinoma, 707 (47%); small-cell carcinoma, 271 (18); squamous-cell carcinoma, 256 (17); large-cell carcinoma, 75 (5); unspecified NSCLC, 151 (10); other, 45 (3)
Meinhold, 2010 (USA) (57)	Case–control (MLCS) 1998–ongoing	Cases, 66 [58–73]; hospital controls, 64 [56–71]; population controls 67 [61–72] ⁱ	430/316 (hospital controls) + 295 (population controls)	NSCLC, 430 (100)
Paulus, 2010 (USA) (28)	Case–control (LCSS) 1992–2003	Cases, 66 [11]; controls, 58 [11]	1004/848	Adenocarcinoma, 455 (45); squamous-cell, 150 (15); bronchioloalveolar, 121 (12); other, 278 (28)

ATS, American Thoracic Society; CWLCS^b, Czech Women's Lung Cancer Study; ICD, International Classification of Diseases; JPHC, Japanese Public Health Center; LCSS, Lung Cancer Susceptibility Study; MLCS, Maryland Lung Cancer Study; MVA, Motor Vehicle Administration; NBSS, National Breast Screening Study; NHS, National Health System; NR not reported; NSCLC non-small cell lung cancer; NuHS, Nurses Health Study; RCGP OCS, Royal College of General Practitioners Oral Contraception Study; SD, standard deviation; SEER, Surveillance Epidemiology and End-Results; SCHS, Singapore Chinese Health Study; SWHS, Shanghai Women's Health Study.

^a Numbers have been rounded to the nearest integer.

^b Mean age [SD], unless otherwise indicated.

^c Some descriptive data extracted from [58].

^d Individuals (%) in each age stratum.

^e Some descriptive data extracted from [59].

^f Number (percentage) of cases in each age stratum.

^g Percentage of total person-time in each age stratum.

^h Mean age over follow-up [range].

ⁱ Median [interquartile range].

were hospital-based (7 out of 11), and one case–control study was nested in an enumerated cohort. Regarding statistical analyses, the model building and selection process were generally not fully reported. One study did not report risk estimates accounting for participant age. Two studies exclusively included never smokers; of the remaining 14 studies, three did not report estimates from analyses accounting for participants' personal smoking history. Two studies reported estimates for the effect of parity adjusted for other reproductive risk factors. Among the eight studies that used a matched case–control design, age was the most common matching variable.

3.3. Evidence synthesis

It was deemed that a linear model is appropriate for the data (Supplementary Figure). The point estimates of the per-study dose–response coefficients ranged from a protective effect, RR = 0.84 (95% CI, 0.74, 0.96) to a strong harmful effect; RR = 1.31 (95% CI, 1.09–1.57) per livebirth. Overall, there was substantial between-study heterogeneity ($p_Q < 0.001$; $I^2 = 73\%$). The random effects summary RR was 0.98 (95% CI, 0.95–1.02), suggesting that a large effect of parity on lung cancer risk is unlikely (Fig. 2).

3.4. Subgroup analyses

Heterogeneity remained significant when we examined subgroups stratified by study design, the reporting of histology information or the types of statistical analyses performed (Table 2). Heterogeneity could not be explained by study design: the

summary estimates from case–control RR = 0.99 (95% CI, 0.94–1.04) and cohort studies, RR = 0.97 (95% CI, 0.92–1.03) were almost identical. Excluding studies that did not report estimates from analyses accounting for participants' personal smoking history did not significantly affect the summary result, RR = 0.98 (95% CI, 0.94–1.02; $p = 0.29$). Studies not including tumors of small-cell lung cancer histology suggested a protective effect of parity, RR = 0.94 (95% CI, 0.88–1.00; $p = 0.06$), whereas there was no effect among studies that reported including at least some patients with SCLC, RR = 1.00 (95% CI, 0.98–1.03; $p = 0.72$). Meta-regression analyses did not identify any study-level characteristic to explain between-study heterogeneity (Table 3) with the exception of tumor histology: studies limited to tumors of NSCLC histology provided estimates of the per-child RR that were lower than those of studies reporting on mixed histologies. The ratio of the RRs was 0.93 (95% CI, 0.86–1.00; $p = 0.05$). We did not perform meta-analyses stratified by smoking status because this information was inconsistently reported in the primary studies and any such analyses would have been susceptible to reporting bias.

3.5. Potential for bias and sensitivity analysis

There was no evidence that estimates of the dose–response relationship were systematically different between more precise and less precise studies (Egger test p -value = 0.94).

The summary estimate was robust to different methods for assigning exposure levels to the open-ended exposure categories or to the exclusion of these categories: the summary RR always remained close to 1 and the association was non-significant in

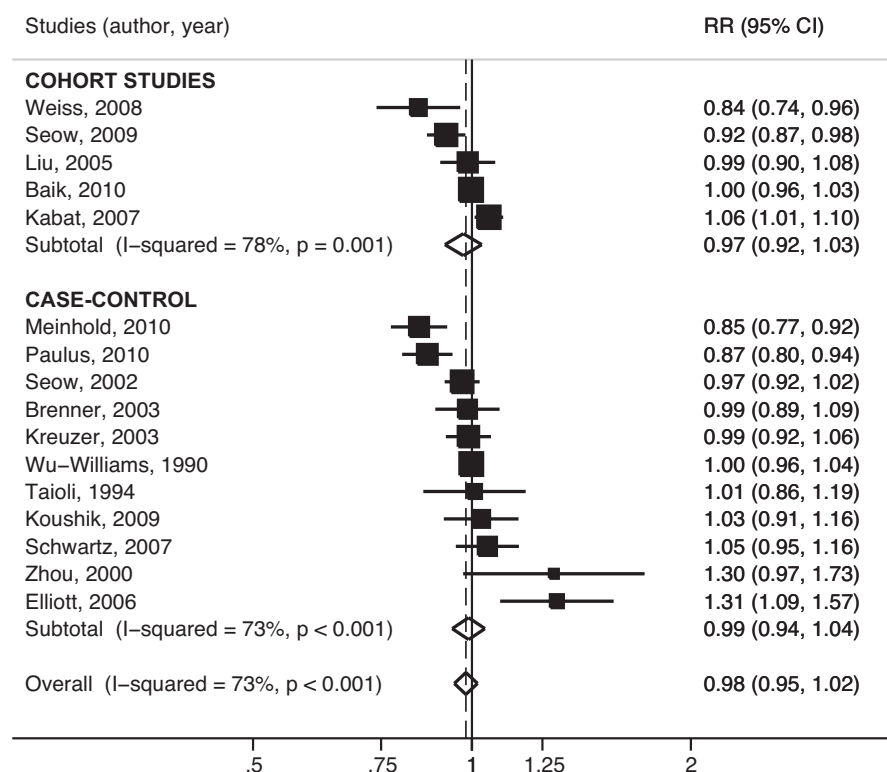


Fig. 2. Forest plot for the meta-analysis of parity and lung cancer risk. Each study is shown by the point estimate of the RR (square proportional to the weight of each study) and 95% CI for the RR (extending lines); summary RRs and 95% CIs by random effects calculations are depicted as diamonds. Point estimate values higher than 1 indicate that increasing parity is associated with increased lung cancer risk. Results are stratified by study design (case-control versus cohort) and then studies are listed by their reported per-child relative risk. CI, confidence interval; RR, relative risk.

all cases. In addition, the results remained robust when repeating the meta-analysis by excluding each study in turn and when the summary RR was obtained through fixed effects calculations, RR= 0.99 (95% CI, 0.97–1.00; *p* = 0.11).

4. Discussion

Given the worldwide increase in lung cancer-related mortality, particularly among women, there is great interest in identifying

risk factors that affect disease risk among women. Parity is an interesting candidate exposure because it is reliably assessed using survey methods and recent evidence has suggested that increasing parity may be inversely associated with lung cancer risk. Our systematic review of 16 epidemiological studies investigating the association of parity with lung cancer indicates that any effect of parity is likely to be small. We identified extensive between-study heterogeneity that remained largely unexplained in

Table 2
Results of main and subgroup analyses for the association of parity and lung cancer risk.

Comparison	Number of studies	Heterogeneity (<i>p</i> _Q ; <i>I</i> ²)	OR (95% CI); <i>p</i> -value
All studies	16	<0.001; 73%	0.98 (0.95–1.02); 0.31
Study design			
Case-control	11	<0.001; 73%	0.99 (0.94–1.04); 0.69
Cohort studies	5	0.001; 78%	0.97 (0.92–1.03); 0.36
Ethnicity			
Non-East Asian	8	<0.001; 83%	0.99 (0.93–1.06); 0.06
East Asians	7	0.04; 54%	0.97 (0.93–1.01); 0.13
Histology			
Did not report including SCLC	8	0.002; 69%	0.94 (0.88–1.00); 0.06
Included SCLC	7	0.33; 13%	1.00 (0.98–1.03); 0.72
Histological confirmation available for ≥80%			
No/NR	6	<0.001; 81%	0.97 (0.89–1.06); 0.49
Yes	10	<0.001; 69%	0.99 (0.95–1.03); 0.58
Details on parity modeling			
No/unclear	8	<0.001; 72%	1.00 (0.94–1.06); 0.91
Yes	8	<0.001; 77%	0.97 (0.92–1.02); 0.27
Adjustment for smoking			
No	3	0.15; 47%	1.00 (0.92–1.09); 0.98
Yes	13	<0.001; 77%	0.98 (0.94–1.02); 0.29
Adjustment for age			
No	1	NA	1.00 (0.96–1.03); 0.87
Yes	15	<0.001; 75%	0.98 (0.94–1.02); 0.37

CI, confidence interval; NA, not applicable; NR, not reported; OR, odds ratio; SCLC, small-cell lung cancer. For some subgroups, the number of studies does not add up to 16 when studies did not report relevant information.

Table 3

Meta-regression results for the association of parity with lung cancer risk.

Covariate assessed in meta-regression	Relative RR (95% CI)	Interaction <i>p</i> -value
Study design (case–control vs. cohort)	0.98 (0.87–1.10)	0.66
Ethnicity (East-Asian vs. non-East Asian)	0.97 (0.86–1.10)	0.63
Lung cancer histology (exclusively NSCLC vs. inclusion of SCLC)	0.93 (0.86–1.00)	0.05
Histological confirmation available for $\geq 80\%$ (yes vs. no/NR)	1.02 (0.91–1.15)	0.66
Details on parity modeling (reported vs. not)	0.97 (0.87–1.08)	0.57
Adjustment for smoking (yes vs. no)	0.97 (0.83–1.13)	0.65
Adjustment for age (yes vs. no)	0.99 (0.81–1.20)	0.88
Proportion of adenocarcinomas among cases (continuous)	1.20 (0.91–1.59)	0.17
Proportion of never smokers among cases (continuous)	0.95 (0.80–1.13)	0.56
Proportion of never smokers among non-cases (continuous)	0.97 (0.72–1.31)	0.85
Enrollment start year (continuous)	1.00 (0.99–1.00)	0.16
Publication year (continuous)	1.00 (0.99–1.00)	0.34

CI, confidence interval; NR, not reported; NSCLC, non-small cell lung cancer; RR, relative risk; SCLC, small-cell lung cancer. Confidence intervals and *p*-values were derived from Student's *t*-distribution.

subgroup and meta-regression analyses. In meta-regression analyses, the only study level characteristic with suggestive evidence that it modified the association between parity and lung cancer was the inclusion of tumor histologies other than NSCLC among cases.

Although the findings regarding histology are intriguing, they need to be interpreted with caution. Given the large number of exploratory analyses that we performed, the borderline *p*-value and the small magnitude of the interaction effect should at best be considered hypothesis-generating observations [48]. Nonetheless, future studies may benefit from exploring better defined disease subgroups, by limiting analyses to NSCLC or performing subgroup analyses by histology (adenocarcinoma versus other NSCLC) [28].

By its very nature, a meta-analysis inherits all the shortcomings of the constituent studies. We observed extensive clinical and methodological variability among the included studies. For case–control studies not nested within an enumerated cohort, control sampling strategies were quite variable. Because reporting of patient characteristics was often incomplete, comparing analyzed populations across studies is challenging. Further, most studies did not describe how the final regression models were built or how their performance was evaluated. Thus, it is not possible to deduce if there is risk of selective reporting. There was also substantial heterogeneity in the statistical analyses, especially regarding the potential confounders included in the final models, and their functional form.

Because the mean or median age of control participants was relatively low and lung cancer appears most often in ages over 70 years, some outcome misclassification may have ensued. However, lung cancer is a rare disease and it is unlikely that misclassification affected study results substantially, or could explain between-study heterogeneity. Furthermore, given that any effect of parity is expected to be small, and the fact that age and tobacco smoking are strongly associated with lung cancer risk, there is a high risk of residual confounding, particularly in studies that did not adjust for these factors or for those that adjusted in incomplete ways [49]. Hormonal and reproductive characteristics are associated with differences in smoking behavior in many populations, and other environmental exposures, age or socio-economic status may confound or interact with the effect of parity on lung cancer risk. Particularly in East Asian countries, female sex is associated with exposures such as indoor air pollution from cooking fumes that may further influence the association of parity with lung cancer and deserve consideration as potential confounders [50–53]. Inadequate control for confounding and lack of consideration of potential interaction effects may have influenced the results of individual studies as well as our estimation of the average parity effect [54–56].

In view of recently published studies supporting a protective effect of parity on lung cancer risk [28,29,57], along with our finding that tumor histology may modify this association, further research may be warranted. However, it is doubtful whether conducting yet another epidemiological study will help explain the substantial between-study heterogeneity we quantified. Arguably, the best way to explore and explain between-study heterogeneity is through a collaborative re-analysis (meta-analysis) of individual participant data from existing studies after standardizing definitions of the exposures and outcomes of interest and a common, *a priori* agreed upon analytical plan. Further, a meta-analysis of individual patient data would provide a more definitive estimate of the association between parity and lung cancer risk. It would also offer the opportunity to powerfully address additional hypotheses regarding lung cancer risk, if necessary data are available.

Several limitations need to be considered when interpreting our results. First, we did not have access to the primary data from most of the studies included in the meta-analysis and could not perform additional adjustments for potentially important covariates. Differences in statistical adjustments across studies may account for some of the unexplained between-study heterogeneity [49]. In addition, because the parity distribution in each included study was unavailable, we could not accurately assign an exposure value to open-ended parity categories [40]. This is a common limitation in studies of dose–response relationships based on aggregate data. However, our results remained robust to sensitivity analyses to different methods of assigning exposure values to open ended categories, indicating that the assignment did not have undue influence on our results [41].

In conclusion, our review identified substantial heterogeneity among studies of the effect of parity on lung cancer. Study design features, participant ethnicity or aspects of study quality could not explain this variability. There was some indication that the histology of lung cancer cases affected study results, suggesting that future studies should be limited to – or provide separate results by – specific histological subtypes. A collaborative re-analysis of primary data from the individual studies, after standardizing exposure and outcome definitions and developing a uniform approach for confounding control will help explore and explain the observed between-study differences, and would be in the position to provide a more definitive answer regarding the parity–lung cancer association.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.lungcan.2011.10.014.

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