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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.

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 carcinogenetic 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 carcinogenetic 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 livebirth 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