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Reproductive factors and lung cancer risk among women in the Singapore Breast Cancer Screening Project

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ABSTRACT

Objectives: A growing body of literature suggests that female hormones play a role in lung cancer risk. Our study aims to examine the relationship between reproductive factors and lung cancer incidence in a large prospectively enrolled cohort in Singapore.
Materials and Methods: Multivariate Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of lung cancer for each exposure, adjusting for smoking, age at entry, ethnicity and body mass index.
Results: Among 28,222 women aged 50–64 years enrolled in the Singapore Breast Cancer Screening Project from October 1994 to February 1997, we identified 311 incident lung cancer cases (253 in non-smokers) over an average of 15.8 years of follow-up to 31 December 2011. Higher parity was associated with decreased lung cancer risk. Compared with nulliparous women, those with 1–2, 3–4, and ≥5 deliveries had a hazard ratio (HR) of 0.56, 0.55 and 0.45, respectively ($P_{trend} < 0.01$). This association was observed in both smokers and non-smokers, and in both adenocarcinomas and non-adenocarcinomas. Reproductive period, breastfeeding, oral contraceptive and hormone replacement therapy use did not seem to influence the risk of getting lung cancer.
Conclusion: Our findings add to the existing evidence that parous women have a lower lung cancer risk than nulliparous women.

1. Introduction

Lung cancer is the leading cause of cancer mortality both worldwide [1] and in Singapore [2]. Despite low rates of smoking, the incidence of lung cancer among Singapore women remains high [2], with a significant proportion of cases occurring among non-smokers [3]. Adenocarcinoma of the lung, the subtype least influenced by cigarette smoking, is also the predominant histological subtype of lung cancer in these women [4]. These gender differences have led to speculation about a possible role for female hormones in lung carcinogenesis.

The biological plausibility of hormonal involvement in lung carcinogenesis is supported by pre-clinical studies that identified estrogen and progesterone receptors in human lung cancers [5,6], and a significantly higher expression exhibited by adenocarcinomas than other lung cancer cell types [7]. There are also a considerable number of epidemiologic literature on the association between lung cancer and reproductive factors including: parity, menstrual history, age at menopause, age at menarche, oral contraceptive (OC) and hormone replacement therapy (HRT) use. However, findings are generally inconsistent, with reports of increased and decreased risk associated with the factors investigated [8–44]. These inconsistencies may reflect differences in study populations, varying adjustments of covariates, or chance associations due to small sample size. In the latest report from the Women's Health Initiative (WHI) studies, the authors have

Abbreviations: HDB, housing development board; HRT, hormone replacement therapy; ICD-9, International Classification of Diseases, Ninth Revision; ICD-O, International Classification of Disease for Oncology; ILCCO, International Lung Cancer Consortium; OC, oral contraceptive; SBCSP, Singapore Breast Cancer Screening Project; WHI, Women's Health Initiative.

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concluded no strong association between female lung cancer and reproductive history or hormone use [44].

In Singapore, two hospital-based case control studies [13,39] and a cohort study [28] have examined this question. Results from these studies are consistent with regard to a protective effect of high parity against lung cancers, with the effect more evident in non-smokers. Longer menstrual cycle was shown to be inversely associated with lung cancer risk in the first case-control study [13]. In the second case-control study [39], the authors additionally found an increased risk associated with later age at first birth, later age at menopause and longer reproductive period.

We used data retrospectively from a large cohort study to examine reproductive factors and exogenous hormone use in relation to lung cancer incidence in the Singapore Breast Cancer Screening Project.

2. Materials and methods

2.1. Singapore Breast Cancer Screening Project (SBCSP)

SBCSP is a population-based randomized controlled trial of mammography screening for breast cancer conducted between October 1994 and February 1997. Methods for the study have been described in detail elsewhere [45]. Briefly, women aged 50–64 years were identified from a comprehensive population registry (n = 166,600), and were randomized to receive either 2-view mammography without physical examination, or observation over 2 years. A total of 69,473 women were randomly selected for 2-view mammography. Pregnant women, or women who had cancers, mammography, or breast biopsy prior to screening, were excluded from screening. In all, 28,234 women were screened by mammography. The SBCSP was supported by the Ministry of Health, Singapore.

2.2. Study population

We used the cohort of women enrolled in the screening mammography arm to evaluate retrospectively the association between reproductive factors and lung cancer incidence. Among the 28,234 participants, we excluded 3 women with a history of lung cancer during the initial screen, and 9 women with transcription errors in their records, leaving 28,222 women in this analysis. Date of entry into the study was defined as the date at which the baseline questionnaire was completed and follow-up time calculated as the time between study entry and the earliest of: (a) 31 December 2011, (b) the date of diagnosis of lung cancer, or (c) the date of death from any cause. During the 15.8 years of follow-up, a total of 311 women developed lung carcinomas.

2.3. Exposure ascertainment

Prior to mammography, participants completed a structured questionnaire that gathered information on demographic characteristics, lifestyle factors, and reproductive history. Demographic and lifestyle information collected included date of birth, ethnicity, education level, marital status, housing status, occupational status, height and weight, anthropometric measurements, smoking habits, and family history of breast cancer. Reproductive history collected included ages at menarche and menopause, pregnancy and delivery histories, ages at first and last delivery, breastfeeding history, and the use of exogenous hormones.

2.4. Case ascertainment

Incident lung cancer cases from the date of baseline interview until 31 December 2011 were identified by record linkage with the Singapore Cancer Registry and the Registry of Births and Deaths. Using histology codes from the International Classification of Diseases, Ninth Revision (ICD-9), and the International Classification of Disease for Oncology (ICD-O), all primary incident cancers of the bronchus and lung (ICD-9 162.0–162.9) were considered for the present analysis. Lung carcinomas included small cell (8041/3), adenocarcinoma (8140/3,8260/3,8310/3,8480/3,8481/3), squamous cell (8070/3), non-small cell (8046/3), large cell (8012/3,8013/3), undifferentiated (8020/3), and other or not otherwise specified (NOS) carcinomas (8000/3, 8001/3, 8010/3, 8022/3, 8033/3, 8240/3, 8246/3, 8250/3, 8252/3, 8253/3, 8255/3, 8550/3, 8560/3).

2.5. Statistical analysis

Descriptive statistics were used to summarize the baseline demographic characteristics of the study population: Pearson χ^2 or Fisher's exact test for categorical variables, and Student's t-test for continuous variables. The Cox proportional hazard regression model, with person-years of follow-up as the time scale, was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of developing lung cancer. Proportional hazard assumptions for exposures and other variables included in the statistical model was tested using Schoenfeld and scaled Schoenfeld residuals method and revealed no departures. Tests for linear trends across the exposure categories were carried out by treating these categorical variables as ordinal variables. Likelihood ratio test was used to test for interaction between factors. The final multivariate Cox model was developed on the basis of biologic relevance and statistical criteria. Our final models adjusted for age at entry, ethnicity, body mass index, smoking status and smoking intensity. HR estimates were also obtained separately from analyses stratified by smoking status (non-smokers and ever-smokers) and histology subtypes (adenocarcinoma and non-adenocarcinoma). All tests of statistical significance were two-sided with significance level set at 0.05. We used STATA version 11.0 (STATA Corp., Texas, USA) for data analyses.

3. Results

A total of 28,222 women contributed 446,182 person-years of follow-up. Most of the study participants were Chinese (84.2%) and were non-smokers (93.8%). Compared to non-cases, lung cancer cases have a higher mean age at entry (58.86 vs 57.91 years), lower body mass index (BMI) (24.08 vs 24.76), and a lower waist-to-hip ratio (WHR) (0.81 vs 0.82). Chinese accounted for 92.93% of the cases and 84.11% of non-cases, and there were more smokers among the cases (18.65%) compared to non-cases (6.06%). When restricted to non-smokers, cases are more likely to be Chinese (92.09% vs 83.69%) and to have a smaller WHR (0.81 vs 0.82). Among smokers, cases were generally older during study entry (61.34 vs 59.31 years) and have a lower BMI (22.47 vs 24.43). Adenocarcinoma accounted for more than half of the total cases (63.67%), small cell carcinoma for 10.29%, squamous cell carcinoma for 4.5%, and other cell types for 21.54%. The proportion of adenocarcinoma was higher among non-smokers (69.17%) than among smokers (39.66%) (Table 1).

Compared to nulliparous women, those parous had a significantly lower risk of lung cancer. The HR was 0.56 (95% CI: 0.38, 0.82) for women who had 1 or 2 deliveries compared to nulliparous women, and there was a trend toward decreasing risk with increasing parity, reaching a HR of 0.45 (95% CI: 0.30, 0.70) in women who have had ≥5 deliveries ($P_{trend} < 0.01$). Differences between categories of parous women, however, were small. Amongst parous women, ages at first delivery and last delivery did not impose

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