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Active cigarette smoking and the risk of breast cancer: a cohort study

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ABSTRACT

Background: Tobacco use has been implicated in the etiology of a large number of cancers, and there exists substantial biological plausibility that it could also be involved in breast carcinogenesis. Despite this, epidemiological evidence to date is inconsistent. The aim of this study was to investigate the role of active smoking and the risk of incident, invasive breast cancer using a prospective cohort of women from the Canadian Study of Diet, Lifestyle and Health.

Methods: Using a case-cohort design, an age-stratified subcohort of 3314 women was created from 39,532 female participants who returned completed self-administered lifestyle and dietary questionnaires at baseline. A total of 1096 breast cancer cases were identified in the entire cohort (including 141 cases from the subcohort) by linkage to the Canadian Cancer Registry. Cox regression models were used to estimate hazard ratios for the association between the different smoking exposures and the risk of breast cancer, using a modification for the case-cohort design.

Results: After carefully considering early-life exposures and potential confounders, we found no association between any smoking exposure and risk of breast cancer in this study (Hazard ratio = 1.00, 95% confidence interval = 0.87–1.17 for ever vs never smokers).

Conclusions: Although these results cannot rule out an association between smoking and breast cancer, they do agree with the current literature suggesting that, if an association does exist, it is relatively weak.

1. Introduction

Tobacco consumption is the single greatest avoidable risk factor for cancer and is estimated to be causal for 21% of all cancer mortality worldwide [1]. In addition to the well-established effects of tobacco smoke on lung carcinogenesis, there is also strong evidence that cigarette smoking is associated with increased risk of many other cancers, including laryngeal, bladder, bowel, kidney, cervix, esophageal and gastric, indicating that it has extensive systemic effects [2]. Breast cancer has also been implicated because mammary tissue is capable of uptake of many tobacco carcinogens routinely found in systemic circulation, including polycyclic aromatic hydrocarbons, aromatic amines and *N*-nitrosamines [3]. Mammary epithelial cells can subsequently metabolize and activate these compounds into electrophilic intermediates capable of DNA damage and adduct formation [4,5]. Smokers have a higher prevalence of these tobacco-related DNA adducts and also p53 gene mutations than non-smokers, and genomic alterations of mammary epithelial cells exposed to tobacco carcinogens begin to resemble those seen in familial breast cancer [6,7]. Moreover, substantial evidence exists for tobacco-induced breast tumorigenesis in animal models [3].

Despite the plausible biological association between tobacco smoke and breast cancer risk, epidemiological evidence has remained inconsistent. In 2004, both the International Agency for Research on Cancer (IARC) [8] and the US Surgeon General [9] concluded that the evidence suggested no causal relationship between active smoking and breast cancer, based on studies published up until 2002. More recently however, evidence seems to suggest a weak positive association, and in contrast to these previous reports, the IARC Monographs were updated in 2012 to state that "a positive association has been observed between

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tobacco smoking and cancer of the female breast", based on studies published through 2009 [2]. In agreement with this, the most recent report from the US Surgeon General states that a history of ever smoking is consistent with an increase of relative risk for breast cancer of an estimated 10% [10]. Reviews of the association between smoking and the risk of breast cancer have identified many methodological issues that may have contributed to discrepancies between previous published studies, either masking a small existing association or spuriously creating one [11–13].

Problems in quantifying risk can arise from the misclassification of exposure. Indeed, previous studies have not been uniform in their consideration of duration and intensity of smoking. In addition, as with many risk factors related to breast cancer etiology, the timing of exposure may be important. Breast tissue is most susceptible to chemically-induced carcinogenesis prior to full differentiation, which occurs at the completion of a woman's first full-term pregnancy [14]. Thus, age at initiation of smoking, total duration of smoking, and years smoked prior to first pregnancy have been implicated in breast cancer risk; however, these are all highly correlated with birth cohort and attained age. Moreover, the duration of smoking pre-pregnancy is associated with age at first pregnancy, which itself is a risk factor for breast cancer [15].

The association between smoking and breast cancer can also be affected by other confounding factors. In particular, an important potential confounder of this association is alcohol intake [16]. Alcohol is an established risk factor for breast cancer and is also strongly correlated with smoking [17]. In addition, it has been shown that smokers are less likely to subject themselves to mammograms than non-smokers and, in particular, former smokers, thus creating a potential under-estimation of breast cancer incidence in current smokers [18].

In the present study, we investigated the role of active smoking in the risk of breast cancer using a prospective cohort of Canadian women. We used case-cohort analyses to evaluate associations and were able to consider estimates of early life exposure while also examining confounding by a history of alcohol intake, reproductive variables, and mammography screening.

2. Materials and methods

2.1. Study population

The Canadian Study of Diet, Lifestyle and Health (CSDLH) is a prospective cohort study described elsewhere [19]. Briefly, the study recruited 73,909 Canadian male and female participants, predominantly from alumni of the Universities of Alberta, Toronto and Western Ontario between 1995 and 1998. A small contingent was also recruited through the Canadian Cancer Society, mostly in 1992. At recruitment, participants completed detailed self-administered dietary and lifestyle questionnaires. Incident cases of breast cancer (and other cancers) were ascertained by means of computerized record linkage (using identifying information provided by the study participants for this purpose) to the Canadian Cancer Registry (CCR) and to the Ontario Cancer Registry. The CCR is a collaborative effort between the thirteen Canadian provincial and territorial cancer registries and the Health Statistics Division of Statistics Canada. Because each Canadian province and territory has a legislated responsibility for cancer collection and control, reporting is virtually complete (estimated at 97%) [20]. Migration out of Canada was very low during this period (estimated to be less than 0.005%) [21]. Deaths from all causes were ascertained by means of record linkage to the National Mortality Database, and this information was used as a censoring variable. Follow-up was continued through December 31st 2010 for participants who were resident in Ontario and through December 31st 2005 for participants residing in all other provinces.

2.2. Study design

The analysis reported here was conducted using a case-cohort design. The motivation for using a case-cohort approach was that where the outcomes of interest are relatively rare, as is the case here, this design represents a very cost-effective approach and loses little efficiency compared to a full cohort analysis [22,23]. The study included a total of 1096 incident, invasive breast cancer cases and a subcohort of 3314 women, which was created by selecting an age-stratified random sample of the entire female cohort ($N = 39{,}532$) at baseline. Given that we were to make comparisons between this selected subcohort and cancer cases, the subcohort was sampled with more weight for older participants. Thus, each 5-year age group had a different sampling fraction that increased with age, thereby attempting to approximate the anticipated distribution of age at diagnosis for all incident cancers. All women in the subcohort were followed through either date of death, date of diagnosis (for cases that arose in the subcohort, $n = 141$), or the censoring administrative date (December 31st 2010 for residents of Ontario and December 31st 2005 for residents of all other provinces).

2.3. Cigarette smoking and other known confounding variables

The self-administered lifestyle questionnaire solicited information on a variety of demographic, lifestyle and social factors including height, weight, race/ethnicity, education, physical activity, and medical history including a detailed reproductive history section. Detailed tobacco use was queried in the lifestyle questionnaire, including questions relating to current smoking status, age at starting smoking, and age at cessation, extent of inhalation, number of cigarettes per day (allowing for changes in number of cigarettes during different time periods), and cigar and pipe smoking. Cigarette smoking exposures evaluated in this study were as follows: smoking status (never, ever, former, current), smoking duration in years (none, <10, 10–<20, 20–<30, 30–<40, 40+), smoking intensity in cigarettes per day (none, <5, 5–<10, 10–<15, 15–<20, 20+), total pack-years of smoking (none, <10, 10–<20, 20–<30, 30+), age at starting smoking in years (never, <15, 15–<20, 20–<25, 25+), and number of years smoked prior to first full term pregnancy (calculated among women with at least one full-term pregnancy by subtracting age at starting smoking from age at first full term pregnancy; categorized as none, <5, 5–<10, 10–<15, 15+).

2.4. Statistical analysis

Seven participants (one case and six controls) were missing smoking information and were thus excluded, leaving 1096 cases and 3314 subcohort members contributing to these analyses. Hazard ratios for the association between the different smoking exposures and risk of breast cancer were evaluated via Cox regression models with time on study as the time scale, using a modification for case-cohort analysis as described by Langholz and Jiao [24]. Models were adjusted for known breast cancer risk factors selected a priori. These included birth cohort (pre-1915, 1915–1924, 1925–1934, 1935–1944, 1945–1954, 1955–1964, post-1964) [25], age (years) at menarche (≤12, 13, ≥14), use of oral contraceptives (never/ever), use of hormone therapy (never, estrogen only, estrogen plus progestin, missing or unspecified), number of live births (nulliparous or missing, 1–2, ≥3), age (years)