Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies

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ABSTRACT

Background. The 2014 US Surgeon General's report noted research gaps necessary to determine a causal relationship between active cigarette smoking and invasive breast cancer risk, including the role of alcohol consumption, timing of exposure, modification by menopausal status, and heterogeneity by estrogen receptor (ER) status.

Methods. To address these issues, we pooled data from 14 cohort studies contributing 934 681 participants (36 060 invasive breast cancer cases). Cox proportional hazard regression models were used to calculate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results. Smoking duration before first birth was positively associated with risk (p-value for trend=$2x10^{-7}$) with the highest HR for initiation >10 years before first birth (HR=1.18, CI 1.12–1.24). Effect modification by current alcohol consumption was evident for the association with smoking duration before first birth (p-value=$2x10^{-4}$); compared to never smoking non-drinkers, initiation >10 years before first birth was associated with risk in every category of alcohol intake, including non-drinkers (HR=1.15, CI 1.04–1.28) and those who consumed ≥3 drinks per day (1.85, 1.55–2.21). Associations with smoking before first birth were limited to risk of ER+ breast cancer (p-value for homogeneity=$3x10^{-3}$). Other smoking characteristics were associated with risk even after controlling for alcohol, but were not associated with risk in non-drinkers. Effect modification by menopause was not evident.

Conclusions. Smoking, particularly if initiated before first birth, was modestly associated with ER+ breast cancer risk that was independent of adult alcohol intake. Possible links with breast cancer provide additional motivation for young women to not initiate smoking.

Key Words. Tobacco smoking, alcohol, breast cancer

KEY MESSAGES

- In a pooled analysis of 14 prospective cohort studies of nearly one million women, smoking >10 years before first birth had the strongest association with breast cancer risk of all the smoking characteristics.

- The association with smoking >10 years before first birth varied by alcohol consumption, but was evident in every category of alcohol intake.

- Associations with smoking characteristics, including those with smoking initiation, were stronger for risk of ER+ breast cancer.

- The association of smoking characteristics with breast cancer risk varied little by menopausal status and age at menopause.

BACKGROUND

Determining whether there is a causal relationship between active cigarette smoking and breast cancer risk has been controversial. Strong biological data linking active smoking, particularly at young ages, with breast carcinogenesis, include the induction of mammary cancers by 20 tobacco smoke compounds in rodents [1-3] and detectable tobacco metabolites [4, 5] and smoking-specific DNA adducts and p53 mutation in human breasts[6-10]. Despite the biological data and the large number of epidemiologic studies [1, 2, 11-16] , the recent U.S. Surgeon General's report concluded that "the evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer [11]." The report noted lingering epidemiological issues concerning the assessment of this relationship, including whether the association is due to: (a.) the timing of exposure at early ages and/or long duration of smoking, (b.) confounding or effect modification by alcohol intake, (c.) modification by menopausal status, or (d.) differences by estrogen receptor (ER) status.

The two prevailing concerns are residual confounding by alcohol intake and timing of smoking initiation relative to first birth [1, 2, 11-16]. Alcohol consumption is an established risk factor for breast cancer; even consumption at low levels is associated with increased risk [17]. Some have argued that the association with active smoking can only be evaluated in never drinkers, because of the potential correlation between cigarette smoking and alcohol consumption[18]. The Collaborative Group on Hormonal Factors in Breast Cancer [18] concluded that there was no association of ever smoking (relative risk (RR)=1.03); however, among drinkers, the RR with ever smoking was 1.09, which was attenuated to 1.05 after adjustment for amount of alcohol consumed [18]. Analysis of smoking initiation relative to first birth is also an important issue because before the first full-term birth the undifferentiated breast epithelium is particularly

susceptible to carcinogens [19]. While previous studies have shown that the strongest smoking association with breast cancer risk is among women who initiated smoking prior to first birth [20, 21], no studies have examined associations of initiation relative to first birth stratified by alcohol consumption.

In this study, we pooled data from 14 prospective cohorts and undertook a unified analytical approach to overcome the lingering epidemiological issues related to assessing the association between smoking and breast cancer risk.

METHODS

Study Population. Member studies of the National Cancer Institute (NCI) Cohort Consortium with smoking data and ≥500 incident breast cancer cases were invited to participate; 14 cohorts (Supplemental Table 1) agreed. Investigators from each cohort provided individual-level data for the entire cohort after excluding those who were male, had a personal history of cancer at baseline (except non-melanoma skin cancer), had missing information on smoking status at baseline, or had other cohort-specific exclusions. Data for 934,681 women were included in this analysis. Written informed consent was obtained from study participants at entry into each cohort or was implied by participants' return of the enrollment questionnaire. The present investigation was approved by the Institutional Review Board (IRB) at each participating institution or was considered within the scope of the original IRB protocol.

Exposure Information. De-identified data from the baseline questionnaire were provided for active cigarette smoking, current alcohol consumption (former alcohol drinkers were distinguished for only 6 of 14 studies), and other characteristics. Smoking status (never, former,

current) is defined as at the time the baseline questionnaire was completed. Data were harmonized and variables were categorized *a priori*. Initiation of smoking relative to first birth, defined among parous women, is based on the number of years between age at smoking initiation and age at first pregnancy.

Case Definition. In our primary analyses, cases were defined as incident, invasive breast cancers diagnosed after enrollment and identified through self-report, cancer registry linkage, medical record/pathology report, or death certificate. In the latter situation, breast cancer had to be listed as a primary or contributory cause of death (ICD-9: 174 or ICD-O, ICD-10: C50). Incident i*n situ* breast tumors were excluded from the case definition, because risk factors for *in situ* breast cancer might differ from invasive breast cancer [22]. Tumors of unknown invasiveness were assumed to be invasive.

Statistical Analysis. Person-time was calculated from the date of the return of the baseline survey until the date of the first-occurring event: breast cancer diagnosis, death, or last follow-up. Women diagnosed with carcinoma *in situ* of the breast were censored at the time of diagnosis. In pooled analyses, Cox proportional hazard regression models were used to calculate minimally-adjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI). All models controlled for study as a covariate and were stratified on age at enrollment. Multivariable-adjusted models included breast cancer risk factors (listed in Table 1), and are shown with and without control for alcohol consumption. Models of time since quitting also included smoking duration. Linear trends with continuous smoking variables were evaluated excluding never smokers. In addition to pooled analyses, a meta-analytic approach was used

assuming a random effects model and weighting the cohorts based on the inverse of the cohort size. Between-study heterogeneity was assessed using the I^2 statistic.

Interaction analyses were conducted using a common reference group to evaluate for effect modification on the multiplicative scale. A p-value for interaction was calculated comparing the -2 log likelihood estimates of models with and without the interaction term(s). The interaction term was the cross-product of the two categorical variables with missing values excluded. Associations were evaluated for subgroups defined by ER status using a joint Cox proportional hazards model [23]. Since data on ER status were not available for all cases, we compared main effect associations using cases with and without ER status to ensure those with data were not a biased sample. In sensitivity analysis, the influence of changes in smoking patterns prior to breast cancer diagnosis were examined by excluding cases that were diagnosed within the first two years of follow-up; this exclusion did not appreciably alter associations (data not shown). Reported p-values are two-sided. Analyses were performed in SAS (version 9.4).

RESULTS

Among 934 681 study participants, 36 060 invasive breast cancer cases were diagnosed. The average age at baseline was 53.9 years, age at first birth was 24.0 years, and number of births was 2.5. Most women were white (91.8%), had at least some college education (62.1%), and were postmenopausal at baseline (60.3%). Current smokers at baseline accounted for 16.2% of participants and they smoked an average of 15.3 cigarettes per day. Former smokers accounted for 30.9% of the participants and they quit smoking, on average, at 37.7 years of age. Most

smokers (73.9%) started smoking before their first birth. Parous smokers who started before first birth, compared to those who started after first birth, were more likely to have smoked for longer (mean 23 vs. 20 years, p-value $<1x10^{-3}$), and to have had their first birth at an older age (mean 24 vs. 21 years of age, p-value $<1x10^{-3}$). Known breast cancer risk factors had expected associations (Supplemental Table 2).

Current smokers were more likely than never smokers to be less educated, premenopausal, current alcohol drinkers, oral contraceptive users, never users of menopausal hormone therapy, and have a lower BMI (Table 1). Former smokers were more likely to have used menopausal hormone therapy than never smokers. Current and former smokers were more likely to drink alcohol at baseline than never smokers.

There was little confounding of the association between smoking status and invasive breast cancer (Table 2): controlling for alcohol intake at baseline changed the HR for current smoking from 1.09 to 1.07 (95% CI 1.04 – 1.10), compared to never smokers. There was no evidence of between-study heterogeneity (Supplemental Figure 1). Associations of other characteristics of smoking showed linear trends (p-values$<1x10^{-3}$; Table 2); however, categorical HRs were within a narrow range of values (e.g., HRs for duration in current smokers ranged from 1.01 – 1.11). Smoking 40 or more cigarettes per day at baseline had the strongest association with risk of breast cancer (HR=1.17, 95% CI 1.05 – 1.31; p for trend=$4x10^{-3}$).

In parous women, those who initiated smoking more than 10 years before their first birth had the highest risk of breast cancer, compared to never smokers (HR=1.18, 95% CI 1.12 – 1.24; Table 2). Results for smoking before first birth did not vary by study (Supplemental Figure 2). To evaluate whether this association was driven by residual confounding from later age at first birth

or longer smoking duration, we conducted stratified analyses by these factors and found similar effects for smoking initiation in each strata (p-value for interaction=0.51 and 0.74, respectively; Supplemental Table 3a and 3b).

Smoking patterns differed by current alcohol consumption (results not otherwise shown): among non-drinkers, 68% women were never smokers, 12% were current smokers, and 20% were former smokers. Among people who drank >2 drinks/day, 28% were never smokers, 33% were current smokers, and 39% were former smokers. Smoking ≥40 years was more prevalent among women who reported drinking >2 drinks per day than not currently drinking, 11.5% vs. 4.1% respectively.

The associations of smoking characteristics with breast cancer risk were modified by current alcohol intake (p-values for interaction<0.05; Table 3). Using a common reference group of never smokers, non-drinkers, former and current smoking was not associated with breast cancer risk among non-drinkers; however, current drinkers consuming two or more drinks per day who were former (HR=1.33, 95% CI 1.19 – 1.49) or current smokers (HR=1.32, 95% CI 1.16 – 1.49) were at slightly greater risk than expected under a multiplicative model (expected HRs=1.22 and 1.23, respectively). Smoking more than 10 years before first birth was associated with breast cancer risk among non-drinkers (HR=1.15, 95% CI 1.04 – 1.28) and in every stratum of alcohol intake (Table 3). Current drinkers consuming ≥3 drinks per day who smoked >10 years prior to first birth (HR=1.85, 95% CI 1.55 – 2.21; Table 3) were at noticeably greater risk than expected under a multiplicative model (expected HR=1.37).

Interactions with menopausal status and age at menopause were also examined (Table 4). The associations with smoking status and smoking initiation relative to first birth did not meaningfully vary by menopause status and age at menopause.

We also examined whether the association with smoking status was different for subtypes defined by ER status (Table 5). Most breast cancers were ER+ (67.4%); the association of smoking characteristics with breast cancer risk overall was similar for those with and without hormone receptor data (results not shown). The association with smoking before first birth differed by ER status, in which the association was stronger for risk of ER+ breast cancer than risk of ER- breast cancer (p-value for tumor heterogeneity=$3x10^{-3}$). Modification of the associations of smoking initiation relative to first birth with breast cancer risk by alcohol intake also was stronger for risk of ER+ breast cancer (data not in tables). Current drinkers consuming 2 or more drinks per day who smoked >10 years prior to first birth (HR=2.02, 95% CI 1.64 – 2.49) were also at greater risk than expected under a multiplicative model (expected HR=1.50).

DISCUSSION

In this large pooled analysis, we addressed the key lingering epidemiologic issues raised in the 2014 US Surgeon General's report [11], including the importance of duration and timing of smoking initiation, the role of alcohol intake, modification by menopausal status, and differences in risk by ER status. We confirmed modest associations of current and former smoking with invasive breast cancer risk. We also showed that the timing of smoking initiation was the smoking characteristic most strongly associated with risk, with initiation more than 10 years before first birth associated with an 18% increased risk of breast cancer among parous ever

smokers, and was evident in non-drinkers and in every stratum of alcohol intake. Those who both initiated smoking more than 10 years before first birth and who were the heaviest drinkers (2 or more drinks per day) were at greatest risk from early smoking initiation (85% higher risk of breast cancer), compared to never smoking non-drinkers. Furthermore, this association was stronger for risk of ER+ breast cancer.

Based on their meta-analysis of 22 case-control and prospective studies [11], the Surgeon General's report concluded that the association for smoking before and after first birth did not differ. In our pooled analysis, we found a dose response with the number of years parous women smoked before their first birth. The association was evident in all strata of age at first birth and of duration of smoking indicating the association was independent of these factors, as previously suggested [11]. The inconsistencies among prior studies might be due to the small number of cases, especially if examining the number of years of smoking prior to first birth, in individual studies and the recent maturity of prospective studies that included birth cohorts who initiated smoking at a young age. Our pooled analysis included six of the prospective studies included in the report [11]. Our results for initiation years before first birth are also consistent with models of carcinogenesis of the breast [19].

We further addressed the concern of residual confounding effects by alcohol intake on the association of smoking with breast cancer risk [1, 2, 11-16] by using statistical control in multivariable models and by stratifying the association into categories of alcohol intake with additional statistical control for amount of alcohol within categories. Statistical control for alcohol intake at baseline only slightly attenuated the relative risks for smoking characteristics in

our study. Consistent with the Collaborative Group on Hormonal Factors in Breast Cancer [18], we observed no association between smoking status at baseline and breast cancer risk among non-drinkers. However, we did observe associations with initiating smoking more than 10 years prior to first birth in non-drinkers and in every stratum of alcohol intake at baseline. We cannot, however, eliminate the possibility that this association is further confounded by alcohol consumption during early adult life, which was not captured by the majority of the studies in our analysis. In the Nurses' Health Study II, women who had higher alcohol intake between menarche and first birth also reported higher intakes at baseline and after first pregnancy compared to women who abstained between menarche and first birth. In their multivariable analyses, alcohol intake before first birth, compared to those abstaining before first birth, was associated with breast cancer risk (per 10-g increase: HR=1.11, 95% CI 1.00 – 1.23), independent of cumulative alcohol intake after first pregnancy [24].

Stronger associations between smoking and breast cancer in premenopausal women has been hypothesized because the morphology of the breast and endogenous hormone levels undergo significant changes during the menopausal transition and other breast cancer risk factors are modified by menopausal status [11]. However, we found no modification by menopausal status, which is consistent with prior studies [25, 26]. In our analysis, smoking initiation prior to first birth and smoking status were not modified by menopausal status. Although the interaction was statistically significant for duration of smoking in current smokers, the lower risk estimated for the women who had ≥40 years and who had not gone through menopause was based on very few cases (n=26) and the adjacent exposure category, women who smoked 20 – 39 years, did not differ across strata of menopause.

Despite initial published hypotheses and early evidence from small studies supporting a stronger association of smoking with ER- breast cancer [11], the findings from our pooled analysis suggest smoking, particularly initiation >10 years prior to first birth, suggest a positive association with risk of ER+, but not ER-, breast cancer. Although more recent data summarized in the report found stronger associations for ER+ breast cancer, they listed a number of limitations among the published studies, including use of case-control data, incomplete control for confounders, and bias due to incomplete assessment of ER status [11]. Our pooled analysis was based on prospective cohort data, we controlled for a large number of known breast cancer risk factors, and we found no bias in the association with smoking among the cases who had ER status compared to those who did not.

Although data pooling provided a large number of study participants, it also presented limitations. Variables were harmonized to be inclusive of all participating cohorts, and we were not able to harmonize all variables. We were not able to define a reference group that excluded passive smokers or lifelong never drinkers, which likely biased our results toward the null. Despite this limitation, we did not find evidence of between-study heterogeneity in the associations (Supplemental Figure 1 and 2). We only collected baseline data on smoking status and covariate information. Although current smokers at baseline may have quit during follow-up, one of the studies included here did not find differences in results of baseline or updated smoking status [20].

Consistent with previous studies, our estimate of the magnitude of association between smoking status and breast cancer risk is modest. However, this association did not appear to be

confounded by alcohol intake, rather our results support a synergistic relationship between smoking initiation and adult alcohol drinking. Furthermore, we found that longer duration of smoking prior to first birth was associated with risk, and this association persisted in both drinkers and non-drinkers. The associations with smoking were more consistently associated with risk of ER+ breast cancer. Other lingering epidemiologic issues mentioned in the recent U.S. Surgeon General's report do not appear to have a major influence. While the association with breast cancer might be modest relative to the more profound health effects of smoking on lung and other cancers, the number of breast cancer cases attributable to smoking might increase over time as the prevalence of adolescent smoking in U.S. has remained stable since the 1930s [27, 28], and globally smoking initiation at young ages is increasing [29], and a greater proportion of women are delaying childbirth [30]. Continued research in this area is warranted to further support public health campaigns aimed at preventing smoking and encouraging early cessation.

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