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REVIEW

Active Smoking and Breast Cancer Risk: Original Cohort Data and Meta-Analysis

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Background The relationship between active cigarette smoking and breast cancer risk remains controversial because of unresolved issues of confounding and dose response.

Methods To investigate these issues further, we analyzed data from 73 388 women in the American Cancer Society's Cancer Prevention Study II (CPS-II) Nutrition Cohort. Analyses were based on 3721 invasive breast cancer case patients identified during a median follow-up of 13.8 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from multivariable-adjusted Cox proportional hazard regression models. *P* values were two-sided. We also conducted meta-analyses of our results with those published from 14 other cohort studies.

Results In CPS-II, incidence was higher in current (HR = 1.24, 95% CI = 1.07 to 1.42) and former smokers (HR =1.13, 95% CI = 1.06 to 1.21) than in never smokers. Women who initiated smoking before menarche (HR = 1.61, 95% CI = 1.10 to 2.34) or after menarche but 11 or more years before first birth (HR = 1.45, 95% CI = 1.21 to 1.74) had higher risk (P_{trend} = .03). No relationships were observed with other smoking parameters. Alcohol consumption did not confound associations with smoking status, although neither current nor former smoking were associated with risk among never drinkers ($P_{interaction}$ = .11). In meta-analyses, current (HR = 1.12, 95% CI = 1.08 to 1.16) and former smoking (HR = 1.09, 95% CI = 1.04 to 1.15) were weakly associated with risk; a stronger association (HR = 1.21, 95% CI = 1.14 to 1.28) was observed in women who initiated smoking before first birth.

Conclusions These results support the hypothesis that active smoking is associated with increased breast cancer risk for women who initiate smoking before first birth and suggest that smoking might play a role in breast cancer initiation.

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Approximately 130 epidemiologic studies and seven consensus reports (1–7) examined the relationship between active cigarette smoking and breast cancer risk. Despite the wealth of data on this issue, there is still no scientific consensus, partly because of concern that the association may be confounded by alcohol consumption (8) and partly because studies have not consistently shown an increase in risk with either duration or intensity of smoking (5). The US Surgeon General last reviewed the literature in 2004 and concluded, "The evidence is suggestive of no causal relationship" (4). The International Agency for Research on Cancer reexamined the evidence available through 2009 and concluded that there was "[l]imited evidence of carcinogenicity" (5). However, a quantitative review of published data has not been conducted, although a number of studies have been published in the last 10 years with long-term follow-up, large case ascertainments, and prospective collection of active smoking behaviors (9–17).

The biological data linking active smoking and breast cancer are more conclusive. Tobacco smoke contains at least 20 chemical compounds that induce mammary cancers in rodents (3,4,18). Some of these compounds are lipophilic, and are deposited and stored in breast adipose tissue and later metabolized and activated by mammary epithelial cells (19–21). Women who smoke have detectable smoking metabolites in their breast fluid (22,23) and a higher prevalence of smoking-specific DNA adducts and p53 mutation smoking signatures in breast tissue than do nonsmokers (24–28). Although it has been hypothesized that the effects of active smoking on tumor initiation may be masked by smoking's antiestrogenic effects (29,30), the latter effects are based on indirect evidence, including observations from some studies that smokers have an earlier age at natural menopause (29), higher risk of osteoporosis (31,32), lower risk of endometrial cancer (33), and possibly lower postmenopausal mammographic density (34,35). However, a large pooled analysis found heavy smokers had higher, not lower, circulating levels of estrogens and androgens (36). Thus, the proposed antiestrogenic effect of active cigarette smoking remains hypothetical.

We examined the relationship between active cigarette smoking and invasive breast cancer risk and evaluated this association for

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confounding by alcohol intake in the American Cancer Society's Cancer Prevention Study II (CPS-II) Nutrition Cohort. We also conducted meta-analyses of the results from published cohort studies of active smoking and breast cancer incidence.

Methods

Description of Cohort

Women in this analysis were drawn from the 97 786 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality established in 1992 as a subgroup of a larger mortality study initiated in 1982 (37). At enrollment, the CPS-II Nutrition Cohort members were aged 50–74 years. All participants completed a mailed baseline questionnaire. Follow-up questionnaires were sent to cohort members every two years, starting in 1997, to update exposure information and ascertain newly diagnosed cancer outcomes. The response rate for each of these follow-up questionnaires through 2005 was at least 86%. Informed consent for participation was assumed based on completion and return of study questionnaires. The Emory University School of Medicine Institutional Review Board approves all aspects of CPS-II.

Population for Analysis

Individuals were excluded from the analytical dataset if they were alive at the time of the first survey mailing yet returned no surveys during follow-up (n = 3116), reported a history of cancer in 1992 (except nonmelanoma skin cancer, n = 13 100), had incomplete data on smoking (n = 4588), or did not complete the follow-up survey in 1997 (n = 3555).

Breast Cancer Case Patients

Incident breast cancer diagnoses were self-reported on follow-up questionnaires through June 30, 2007. Invasive breast cancer case patients (International Classification of Diseases, Tenth Revision code: C50) were verified through medical records (n = 2905) or linkage with state registries (n = 684) (21). A small number of case patients (n = 98) were identified during confirmation of other reported cancer diagnoses. Interval deaths were obtained through the National Death Index. Breast cancer deaths (n = 34) were included if the death certificate listed invasive breast cancer as a cause of death (38). Clinical characteristics of the tumor were obtained from state registries or abstracted from medical records.

Exposure Data

Baseline smoking history was based on enrollment questionnaires for the 1982 CPS-II Baseline Mortality Cohort and the 1992 CPS-II Nutrition Cohort and updated in follow-up questionnaires. Baseline smoking status in 1982 was determined based on the response to the question, "Do you now or have you ever smoked cigarettes, at least one a day for one year's time?" Ever smokers were then asked questions on the average number of cigarettes smoked per day, the age when they started smoking, and the total number of years they smoked. Former smokers were also asked their age of smoking cessation. Responses were used to create analytical smoking variables, and categories were selected a priori based on prior smoking literature and the distribution in our study population.

Statistical Analyses

Participants contributed person-time to the analysis until the first censoring event: 1) diagnosed with cancer (including in situ carcinoma of the breast), 2) died before the end of follow-up, 3) failed to complete any survey, or 4) reached the end of follow-up through June 30, 2007. All models were stratified on year of age at enrollment. Extended Cox regression models (39) were used to calculate multivariable-adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and the Wald *P* value. To evaluate the overall effect of smoking status (never, former, current smoker), we also estimated the *P* value for the likelihood ratio test with 2 degrees of freedom. .

Multivariable-adjusted models included age at menarche, age at first birth, menopausal status and age at menopause, alcohol consumption, race, education, body mass index, family history of breast cancer, history of breast cysts, use of postmenopausal hormone therapy, mammogram within 2 years of the questionnaire, and use of oral contraceptives. Smoking status, alcohol status, use of postmenopausal hormones, and use of mammography screening were treated as time-dependent covariables. All Cox models were stratified on year of age at enrollment. The proportional hazards assumption was evaluated by testing for an interaction by time in the model; no violations were observed.

We assessed effect modification by alcohol intake, family history of breast cancer, mammographic screening, body mass index, and postmenopausal hormone use comparing the –2 log likelihood estimates of models with and without the interaction term(s). Associations were evaluated for subgroups defined by estrogen receptor status, histology, and the Surveillance, Epidemiology and End Results (SEER) summary stage using models to predict risk for one subgroup while censoring for the other subgroups. The *P* value for tumor heterogeneity was estimated comparing the –2 log likelihood of a case-only model with and without smoking status as an explanatory variable (2 degrees of freedom likelihood ratio test). In sensitivity analysis, the influence of changes in smoking patterns before breast cancer diagnosis was examined by excluding case patients that were diagnosed within the first 2 years of follow-up. Reported *P* values are two-sided and were considered statistically significant if less than 0.05. *P* values for linear trend were calculated using the appropriate linear contrasts of the model parameters. These analyses were performed with SAS, version 9.2 (SAS Institute Inc., Cary, NC).

Meta-analysis

PubMed searches were conducted to identify studies of the association of active cigarette smoking and breast cancer incidence from prospective cohort studies published in English-language peer-reviewed journals as of November 2012 using search terms "smoking and breast cancer," "tobacco and breast cancer," and "cigarettes and breast cancer." Reference lists of original contributions, review articles (8,40–43), and consensus reports (1–7) were also searched to identify additional articles. Thirty-two articles were identified (9–17,44–66). Articles were excluded if results were based on analyses of breast cancer mortality (n = 7) (49,50,52–54,62,66), were updated with longer follow-up time (n = 7) (51,56–59,61,64), or did not contain sufficient information to estimate the association separately for current and former smoking (n = 4) (55,60,63,65). Data from 14 other articles (study descriptions and abbreviated names in Supplementary Table 1,

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available online) were combined with data from the CPS-II Nutrition Cohort in meta-analyses of active smoking status (9–17,44–48), and eight other articles (9–17) plus our own were combined in a meta-analysis of age at smoking initiation and smoking before first birth. Study-specific hazard ratios (95% CIs) were abstracted from studies for active cigarette smoking, age at smoking initiation (youngest age category), and initiation relative to first birth ("yes" or the most extreme category of number of years before first birth) with nonsmokers as the referent category. Hazard ratios for smoking status from two studies were calculated using published hazard ratios for current smokers from categories of packs per day (44) and for current and former smokers from premenopausal and postmenopausal estimates (46) using a fixed-effects model (67). Five studies (13,44–46,68) did not examine timing of smoking initiation and therefore were not included in the meta-analysis; the Swedish Population Registry cohort only examined age at smoking initiation (48). Summary hazard ratio (95% CI) estimates were calculated using a random-effects model, with each study result weighted by the within- and between-study variances (67). Between-study heterogeneity was assessed by the Conchran Q test (67) and the I^2 (the proportion of variation in the relative risks attributable to heterogeneity). Publication bias was assessed by Begg test (69). The meta-analyses were performed in STATA SE (version 11.0).

Results

Baseline Characteristics of CPS-II Nutrition Cohort

During a median follow-up of 13.8 years, 3721 invasive breast cancer case patients were identified among the 73 388 women in the analytic cohort. At enrollment, 8.2% of women reported current smoking, 35.6% reported former smoking, and 56.2% reported never smoking (Table 1). The age-standardized incidence rates of breast cancer were 474 per 100 000 person-years among current smokers, 485 per 100 000 person-years among former smokers, and 411 per 100 000 person-years among never smokers. On average, current smokers smoked more than twice as many cigarettes per day for twice as long as former smokers. The median age of smoking initiation was similar for both ever smoker groups. Current smokers were less likely to be overweight or obese, have a child at age 30 years or older, experience menopause at age 55 or older, use postmenopausal hormones, or to have received a recent mammogram compared with both never and former smokers. Both current and former smokers were more likely to consume alcohol and to use oral contraceptives compared with nonsmokers (Table 1).

Associations of Active Smoking With Breast Cancer Risk in CPS-II Nutrition Cohort

In multivariable-adjusted models with smoking status as a time-dependent variable, breast cancer incidence was higher in current (HR = 1.24, 95% CI = 1.07 to 1.42) and former smokers (HR = 1.13, 95% CI = 1.06 to 1.21) than in never smokers. These results were similar to those from models that adjusted only for age (Table 2) and to those that excluded the alcohol consumption variable from the model (current smokers: HR = 1.29, 95% CI = 1.13 to 1.48; former smokers: HR = 1.17, 95% CI = 1.09 to 1.25). Results were similar to those in Table 2 when the study population was limited to women who were postmenopausal in 1992 (current smokers: HR = 1.25, 95% CI = 1.08 to 1.44; former smokers: HR = 1.15, 95% CI = 1.07 to 1.23). Exclusion of the first 2 years of follow-up time did not alter the observed multivariable-adjusted hazard ratios (current smokers: HR = 1.26, 95% CI = 1.08 to 1.47; former smokers: HR = 1.14, 95% CI = 1.05 to 1.23). In sensitivity analyses where multivariable models were based on smoking status only in 1992, hazard ratios were not appreciably different (current smokers: HR = 1.24, 95% CI = 1.10 to 1.41; former smokers: HR = 1.13, 95% CI = 1.05 to 1.21).

The association with ever smoking was slightly stronger for women who started smoking at a young age compared with never smokers (Table 2), although the dose–response relationship was not statistically significant. Greater number of years of smoking before first birth were associated with higher risk of breast cancer in analyses restricted to parous women (n = 62 893; P_{trend} = .03). In particular, those who initiated smoking before menarche (HR = 1.61, 95% CI = 1.10 to 2.34) or after menarche but 11 or more years before first birth (HR = 1.45, 95% CI = 1.21 to 1.74) had higher risks of breast cancer than never smokers. Breast cancer associations did not vary with duration of smoking or cigarettes per day in current smokers or by time since last smoked or age at cessation among former smokers (Table 2).

In analyses that stratified on alcohol drinking status (Table 3), breast cancer was associated with current smoking (HR = 1.36, 95% CI = 1.14 to 1.36; HR = 1.37, 95% CI = 0.87 to 2.15, respectively) and former smoking (HR = 1.19, 95% CI = 1.09 to 1.31; HR = 1.26, 95% CI = 1.00 to 1.60, respectively) in women who reported current and former drinking, but not in women who reported never drinking. However, the test for interaction between smoking and alcohol consumption was not statistically significant (P = .11). The relationship between age at initiation and breast cancer risk in never drinkers could not be evaluated because of small case numbers.

The association between smoking status and breast cancer risk was not modified by family history of breast cancer, mammographic screening, body mass index, or postmenopausal hormone use (data not shown). Current and former smoking were associated with higher risk of estrogen receptor–positive, but not estrogen receptor–negative, breast cancer (Table 4), although the differences were not statistically significant (P = .33). Associations were slightly stronger, but not statistically significantly different (P = .76), for ductal breast cancer than for lobular breast cancer (Table 4).

Meta-analysis

In Figure 1, A and B, the summary estimates for current and former smoking, based on 31 198 breast cancer case patients in 15 cohorts totaling 991 100 women, were 1.12 (95% CI = 1.08 to 1.16) and 1.09 (95% CI = 1.04 to 1.15), respectively, with evidence of between-study heterogeneity for estimates of former smoking (P = .004) but not current smoking (P = .38). No publication bias was evident for estimates of current smoking (P = .78) or former smoking (P = .88).

Summary estimates for age at smoking initiation were based on 10 studies with 28 631 breast cancer case patients among 804 986 subjects (Figure 2A), and summary estimates for initiation of smoking relative to first birth were based on nine studies with 28 470

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Table 1. Demographic and smoking characteristics of women at the time of enrollment*

Categories	Never smokers	Current smokers	Former smokers
No. (%)	41 214 (56.2)	6012 (8.2)	26 162 (35.6)
	Median (IQR)	Median (IQR)	Median (IQR)
Age at enrollment, y	62 (58–67)	61 (56–65)	62 (57–67)
Years of smoking	NA	40 (30–45)	20 (10–30)
Cigarettes per day	NA	15 (10–20)	6 (12–20)
Age at initiation, y	NA	20 (18–26)	20 (18–24)
Age quit smoking, y	NA	NA	42 (32–52)
	%	%	%
Self-described white	97.3	97.1	97.7
Age at initiating smoking, y			
≤15	NA	8.5	7.9
16–20	NA	41.2	43.9
21–25	NA	22.5	18.6
≥26	NA	26.8	16.5
Missing	NA	0.9	13.2
Initiation relative to first birth (ever smokers, parous only)			
Before menarche	NA	0.9	1.2
After menarche, ≥11 years before first birth	NA	5.7	6.5
After menarche, 6–10 years before first birth	NA	17.4	20.8
After menarche, ≤5 years before first birth	NA	29.5	27.7
During/after first birth	NA	34.7	22.3
Missing age at initiation	NA	11.8	21.4
Body mass index, kg/m^2			
<18.5	1.7	3.8	1.5
18.5–24.9	48.7	56.8	50.8
25.0–29.9	31.8	28.0	31.0
≥30	16.3	10.3	15.3
Missing	1.6	1.2	1.5
Education			
<High school grad	5.2	7.1	3.9
High school grad	35.1	34.0	27.1
Some college	29.6	32.5	33.4
College grad or more	29.5	25.7	35.0
Missing	0.6	0.7	0.7
Alcohol consumption			
Never drinker	47.8	25.6	23.7
Former drinker	7.7	11.3	9.7
<1 drink/day	33.8	36.5	44.4
1 drink/day	4.8	10.3	11.3
≥2 drinks/day	1.8	12.2	7.6
Missing	4.4	4.1	3.3
Family history of breast cancer			
Yes	14.1	13.0	14.0
History of breast cysts or lumps			
Yes	31.7	31.7	35.4
Age at menarche, y			
<12	19.1	19.9	20.0
12	25.4	24.3	25.1
13	29.6	28.6	29.4
≥14	24.4	25.4	23.9
Missing	1.5	1.8	1.5
Age at first birth, y			
Nulliparous	7.4	8.3	7.6
<20	9.4	12.7	8.1
20–24	46.8	46.6	46.2
25–29	26.5	23.2	28.0
≥30	7.5	6.5	8.1
Missing	2.3	2.7	2.1
Age at menopause, y			
Premenopausal	5.0	5.2	5.2
<50	44.3	54.9	47.4
50–54	38.5	32.5	36.6
≥55	12.1	7.3	10.6
Missing	0.1	0.2	0.1

(Table continues)

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Table 1. (Continued)

Categories	Never smokers	Current smokers	Former smokers
Oral contraceptive use, %			
Never	64.0	55.1	56.3
Ever	34.7	43.3	42.6
Missing	1.3	1.6	1.1
Postmenopausal hormone use			
Never	44.3	48.0	38.6
Current	32.3	27.1	36.9
Former	22.3	23.7	23.4
Missing	1.0	1.2	1.1
Mammogram			
Never or not recent	33.9	46.4	30.3
Recent (≤ 2 y)	65.1	52.4	68.7
Unknown	0.9	1.2	1.0

* NA = not applicable.

case patients among 774 430 subjects (Figure 2B). As shown in Figure 2A, younger age at smoking initiation was associated with a 12% increase in breast cancer risk; the test for between-study heterogeneity was not statistically significant (P = .29). The summary hazard ratio for initiation of smoking before first birth was 1.21 (95% CI = 1.14 to 1.28) (Figure 2B), which was consistent across all the cohorts (P = .62). No publication bias was evident for estimates of age at smoking initiation (P = .25) or initiation relative to first birth (P = .68).

Discussion

In the CPS-II Nutrition Cohort, a prospective study of more than 73 000 predominantly postmenopausal women, the incidence of invasive breast cancer was higher in current or former smokers than in never smokers. The risk was highest in women who initiated smoking at an early age during the period of biological vulnerability before age at first birth. Alcohol consumption did not appreciably confound these associations. However, the elevated risk was confined to current or former alcohol drinkers, although the confidence intervals were wide for never drinkers. Meta-analysis of the CPS-II results together with those from 14 published cohort studies (9–17,44–48) found similar associations between breast cancer risk and smoking status, with a linear positive association between years of smoking before first pregnancy and risk.

In the CPS-II Nutrition Cohort, the relationship between active smoking and breast cancer incidence differs from that observed with other smoking-related cancers in that there are no dose–response relationships with overall longer duration of smoking, greater number of cigarettes smoked per day, or years since quitting. Most of the current smokers in our study had smoked for at least 20 years before enrollment, precluding analyses of short-term current smokers. Similarly, other cohort studies observed little or no linear dose–response relationships for either duration or intensity of smoking or number of years since cessation (9–17,44–48).

The most consistent evidence supporting a causal relationship between cigarette smoking and breast cancer risk is the stronger association observed for women who initiate smoking before age at first birth. Mammary tissue is thought to be more susceptible to genotoxic exposures before completion of the first full-term pregnancy (70) because the terminal ductal–lobular units of the breast are not fully differentiated until the end of gestation (70–73). The relationship with early life smoking that we and others (9–17,48) observed, together with the lack of a consistent relationship between breast cancer risk and smoking later in life, suggests that active cigarette smoking may play a greater role in the initiation than the progression of breast cancer.

Although the association between active smoking and breast cancer is considerably weaker than that of many other smoking-related cancers (5), the relationship is reasonably consistent in well-conducted cohort studies with long follow-up. All but three of the studies included in the meta-analysis (44,45,48) reported multivariable-adjusted hazard ratios for current smokers above the null; in four studies (10,14,16,17) and in ours, the association was statistically significant. The summary estimate for current smoking of 1.12 was included in the confidence intervals of all 15 studies. Associations for former smoking were weaker but still positive in 13 of 15 studies (9–17,44–48), excluding only the Canadian National Breast Screening Study (10) and the Members of a Large Prepaid Health Plan in Northern California (Kaiser2) (44) cohorts, which found no association and an inverse association, respectively, with former smoking (10).

A persistent question in the breast cancer/smoking controversy concerns potential confounding by alcohol consumption. Alcohol consumption, even at low to moderate levels (5,74,75), is a known risk factor for breast cancer. Alcohol consumption also is correlated with cigarette smoking (76), and current smokers, on average, drink more than former or never smokers (76). However, in our study, the association between active smoking and breast cancer incidence was not attenuated by the inclusion of alcohol intake in the multivariable model. The association was statistically significant only in current and former drinkers in analyses that stratified on alcohol consumption, although the confidence intervals for the association in never drinkers were wide. Unfortunately, only two other cohort studies (10,11) examined interactions with alcohol intake; neither study reported a statistically significant interaction. However, a recent report on smoking and mortality from the Million Women Study found the association with breast cancer mortality was attenuated from 1.13 to 1.06 (95% CI = 0.95

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Table 2. Age- and multivariable-adjusted association between active cigarette smoking and breast cancer risk

Category	Case patients	Age-adjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)	Multivariable-adjusted* *P*†
Smoking status				
Never smokers	1966	1.00 (referent)	1.00 (referent)	
Current smokers	233	1.16 (1.02 to 1.33)	1.24 (1.07 to 1.42)	.003
Former smokers	1522	1.18 (1.11 to 1.27)	1.13 (1.06 to 1.21)	<.001
P‡		<.001	<.001	
Age at initiation among ever smokers, y				
Never smokers	1966	1.00 (referent)	1.00 (referent)	
≥26	320	1.12 (1.00 to 1.26)	1.11 (0.99 to 1.26)	.08
21–25	322	1.12 (0.99 to 1.26)	1.07 (0.95 to 1.21)	.25
16–20	796	1.24 (1.14 to 1.35)	1.19 (1.09 to 1.29)	<.001
≤15	145	1.26 (1.06 to 1.49)	1.23 (1.04 to 1.46)	.02
P§		.14	.20	
Initiation relative to first birth among parous, ever smokers				
Never smokers	1740	1.00 (referent)	1.00 (referent)	
Before menarche	28	1.65 (1.14 to 2.40)	1.61 (1.10 to 2.34)	.01
After menarche, ≥11 years before first birth	154	1.71 (1.45 to 2.01)	1.45 (1.21 to 1.74)	<.001
After menarche, 6–10 years before first birth	379	1.29 (1.15 to 1.44)	1.19 (1.06 to 1.34)	.003
After menarche, ≤5 years before first birth	476	1.17 (1.06 to 1.30)	1.17 (1.05 to 1.30)	.004
During/after first birth	394	1.11 (1.00 to 1.24)	1.15 (1.02 to 1.28)	.02
P§		.004	.03	
Duration among current smokers, y				
Never smoker	1966	1.00 (referent)	1.00 (referent)	
1–40	80	1.17 (0.93 to 1.47)	1.26 (1.00 to 1.58)	.047
40–49	97	1.14 (0.93 to 1.40)	1.21 (0.98 to 1.48)	.08
50–73	54	1.22 (0.93 to 1.60)	1.28 (0.97 to 1.68)	.08
P§		.83	.94	
Cigarettes per day among current smokers				
Never smoker	1966	1.00 (referent)	1.00 (referent)	
1–9	40	1.22 (0.89 to 1.66)	1.26 (0.92 to 1.73)	.15
10–19	69	1.03 (0.81 to 1.31)	1.11 (0.87 to 1.42)	.39
20–29	81	1.22 (0.98 to 1.53)	1.31 (1.05 to 1.64)	.02
30–39	18	1.10 (0.69 to 1.75)	1.15 (0.72 to 1.83)	.57
40–90	13	1.40 (0.81 to 2.42)	1.44 (0.84 to 2.50)	.19
P§		.61	.67	
Years since quit among former smokers				
Never smoker	1966	1.00 (referent)	1.00 (referent)	
31–68	486	1.23 (1.11 to 1.36)	1.15 (1.04 to 1.27)	.008
21–30	324	1.12 (0.99 to 1.26)	1.05 (0.93 to 1.18)	.44
11–20	307	1.16 (1.03 to 1.31)	1.12 (0.99 to 1.26)	.08
1–10	278	1.27 (1.12 to 1.44)	1.27 (1.11 to 1.44)	<.001
P§		.56	.15	
Age at cessation among former smokers, y				
Never smoker	1966	1.00 (referent)	1.00 (referent)	
10–39	577	1.20 (1.09 to 1.32)	1.12 (1.02 to 1.23)	.02
40–49	304	1.11 (0.98 to 1.25)	1.05 (0.93 to 1.19)	.45
50–59	321	1.25 (1.11 to 1.41)	1.22 (1.08 to 1.38)	.001
60–89	193	1.22 (1.05 to 1.41)	1.21 (1.04 to 1.41)	.01
P§		.55	.16	
Duration among former smokers, y				
Never smoker	1966	1.00 (referent)	1.00 (referent)	
<1–10	382	1.18 (1.05 to 1.31)	1.12 (1.00 to 1.25)	.05
11–20	396	1.18 (1.06 to 1.31)	1.11 (1.00 to 1.24)	.06
21–30	310	1.18 (1.05 to 1.33)	1.13 (1.00 to 1.27)	.06
31–70	369	1.28 (1.15 to 1.44)	1.26 (1.13 to 1.42)	<.001
P§		.26	.11	

* Multivariable-adjusted models included age (continuous), age at menarche (<12, 12, 13, ≥13 years, missing), age at first birth (<20, 20–24, 25–29, ≥30 years, missing), menopausal status and age at menopause (premenopausal, postmenopausal at age <50, 50–54, ≥55 years, missing age), alcohol consumption (never drinker, <1, 1, ≥2 drinks/day, former, missing/unknown), race (white, black, others or unknown), education (less than high school, high school graduate, some college, college graduate, missing), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2, missing), family history of breast cancer (yes, no), history of breast cysts (yes, no), use of postmenopausal hormone therapy (never, current, former, missing), recent mammogram (never or not current, recent, missing), and use of oral contraceptives (never, ever, missing). Smoking status, alcohol status, use of postmenopausal hormones, and use of mammography screening were treated as time-dependent covariables. CI = confidence interval; HR = hazard ratio.

† Two-sided Wald *P* value.

‡ Two-sided *P* values for the likelihood ratio test with 2 degrees of freedom.

§ Two-sided *P* values for linear trend were calculated using a single term as a continuous variable, excluding the nonsmokers.

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Table 3. Age- and multivariable-adjusted associations of breast cancer with the interaction between alcohol intake and cigarette smoking

Alcohol use at baseline	Smoking status	Case patients	Age-adjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)	Multivariable-adjusted* *P*†
Never drinker	Never smoker	930	1.00 (referent)	1.00 (referent)	
	Current smoker	50	0.98 (0.73 to 1.30)	1.08 (0.81 to 1.45)	.59
	Former smoker	317	1.05 (0.92 to 1.19)	1.04 (0.91 to 1.18)	.57
P‡			.74	.75	
Former drinker	Never smoker	136	1.00 (referent)	1.00 (referent)	
	Current smoker	23	1.20 (0.77 to 1.87)	1.37 (0.87 to 2.15)	.17
	Former smoker	144	1.29 (1.02 to 1.63)	1.26 (1.00 to 1.60)	.05
P‡			.10	.10	
Current drinker	Never smoker	831	1.00 (referent)	1.00 (referent)	
	Current smoker	152	1.23 (1.03 to 1.46)	1.36 (1.14 to 1.62)	<.001
	Former smoker	1015	1.20 (1.10 to 1.32)	1.19 (1.09 to 1.31)	<.001
P‡			<.001	<.001	

* Multivariable-adjusted models included age (continuous), age at menarche (<12, 12, 13, ≥13 years, missing), age at first birth (<20, 20–24, 25–29, ≥30 years, missing), menopausal status and age at menopause (premenopausal, postmenopausal at age <50, 50–54, ≥55 years, missing age), race (white, black, others or unknown), education (less than high school, high school graduate, some college, college graduate, missing), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2, missing), family history of breast cancer (yes, no), history of breast cysts (yes, no), use of postmenopausal hormone therapy (never, current, former, missing), recent mammogram (never or not current, recent, missing), and use of oral contraceptives (never, ever, missing). Smoking status, use of postmenopausal hormones, and use of mammography screening were treated as time-dependent covariables. CI = confidence interval; HR = hazard ratio.

† Two-sided Wald *P* value was calculated.

‡ Two-sided *P* values for the likelihood ratio test with 2 degrees of freedom.

Table 4. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the associations of breast cancer with cigarette smoking status by breast tumor characteristics

	Never smoker		Current smoker		Former smoker	
Tumor characteristics	Case patients	HR* (95% CI)	Case patients	HR* (95% CI)	Case patients	HR* (95% CI)
Estrogen receptor (ER) status						
ER+	1187	1.00 (referent)	130	1.20 (1.00 to 1.45)	946	1.13 (1.04 to 1.24)
ER-	231	1.00 (referent)	19	0.85 (0.53 to 1.36)	152	0.97 (0.78 to 1.20)
P†						.33
Histological type						
Ductal	1352	1.00 (referent)	168	1.24 (1.05 to 1.46)	1,061	1.14 (1.05 to 1.24)
Lobular	253	1.00 (referent)	18	0.83 (0.51 to 1.36)	182	1.04 (0.85 to 1.27)
P†						.76
SEER summary stage						
Localized	1444	1.00 (referent)	178	1.31 (1.12 to 1.54)	1,112	1.13 (1.04 to 1.23)
Regional and distant	470	1.00 (referent)	45	0.93 (0.68 to 1.27)	369	1.12 (0.97 to 1.29)
P†						.67

* Multivariable-adjusted models included age (continuous), age at menarche (<12, 12, 13, ≥13 years, missing), age at first birth (<20, 20–24, 25–29, ≥30 years, missing), menopausal status and age at menopause (premenopausal, postmenopausal at age <50, 50–54, ≥55 years, missing age), alcohol consumption (never drinker, <1, 1, ≥2 drinks/day, former, missing/unknown), race (white, black, others or unknown), education (less than high school, high school graduate, some college, college graduate, missing), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2, missing), family history of breast cancer (yes, no), history of breast cysts (yes, no), use of postmenopausal hormone therapy (never, current, former, missing), recent mammogram (never or not current, recent, missing), and use of oral contraceptives (never, ever, missing). Smoking status, alcohol status, use of postmenopausal hormones, and use of mammography screening were treated as time-dependent covariables. SEER = Surveillance, Epidemiology and End Results.

† Two-sided *P* value for tumor heterogeneity was estimated from the likelihood ratio test using a case-only model.

to 1.18) among women who consumed little to no alcohol (66). Given the modest association observed between active smoking and breast cancer incidence and the emphasis on potential confounding by alcohol consumption in the former meta-analysis of 53 case–control and cohort studies (8), it is important that this issue be examined further.

The CPS-II cohort provides long-term follow-up of birth cohorts of women who began smoking after World War II. The weight of our conclusions are strengthened by the study's prospective design, large sample size, and detailed information on smoking habits and covariables known to be associated with breast cancer.

Our study was not without limitations. We were unable to control for exposure to secondhand smoke in the CPS-II cohort.

In summary, the findings in our cohort and in the meta-analysis of prospective studies support the hypothesis that active smoking increases breast cancer risk, especially when smoking begins at an early age.

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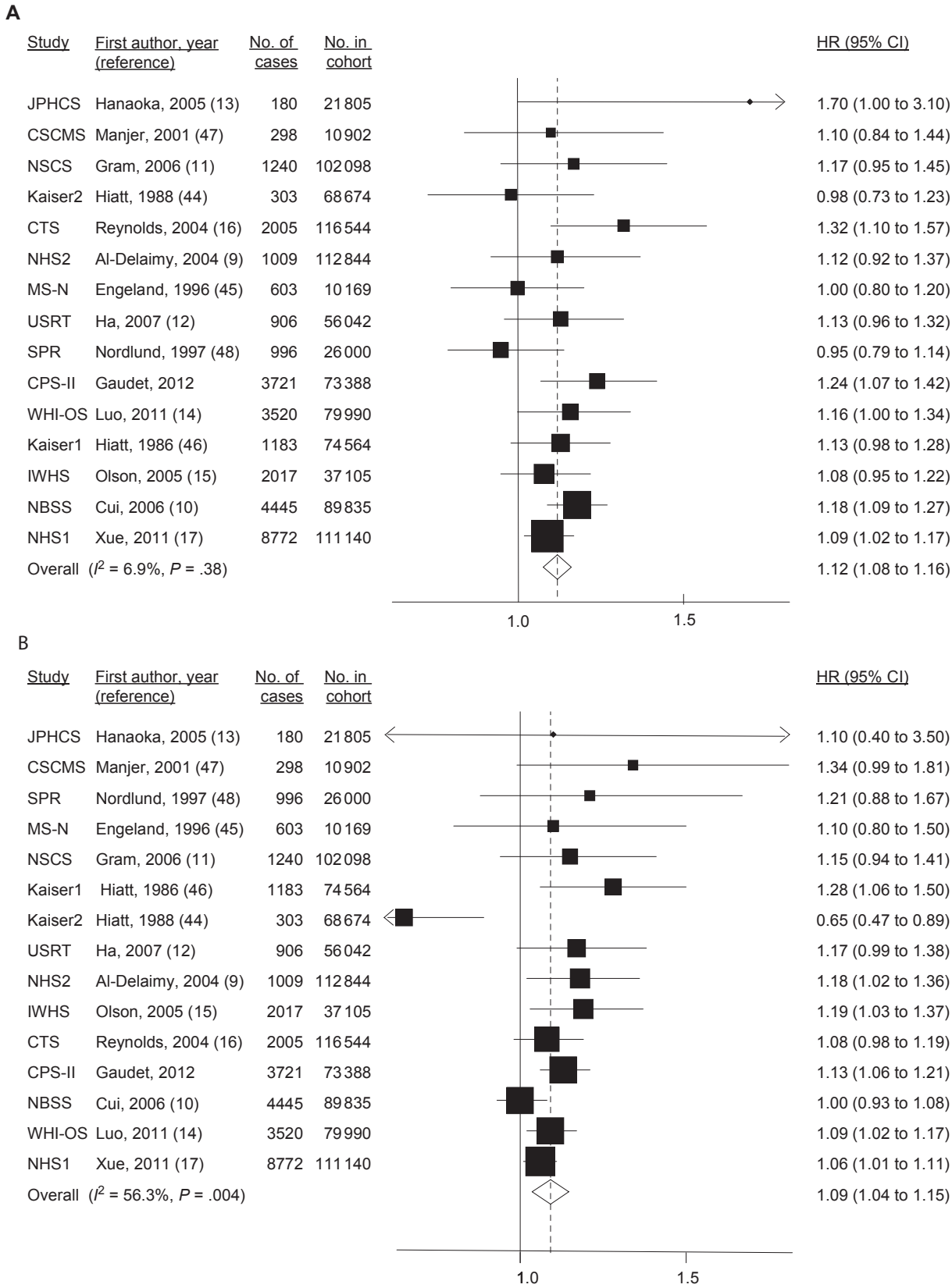

Figure 1. Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of breast cancer associated with current (**A**) and former (**B**) smoking of published cohort studies. Studies are referred to by study abbreviation (defined in Supplementary Table 1, available online), first author, year of publication, and sample size of case patients and cohort and weighted and ranked according to the inverse of the variance of the log hazard ratio estimate. The hazard ratios are represented by the **squares** (the size is proportional to the weights used in the meta-analysis) and the confidence intervals are represented by the **error bars**. The **solid vertical line** represents the null value, and the **dotted vertical line** represents the overall summary estimate.

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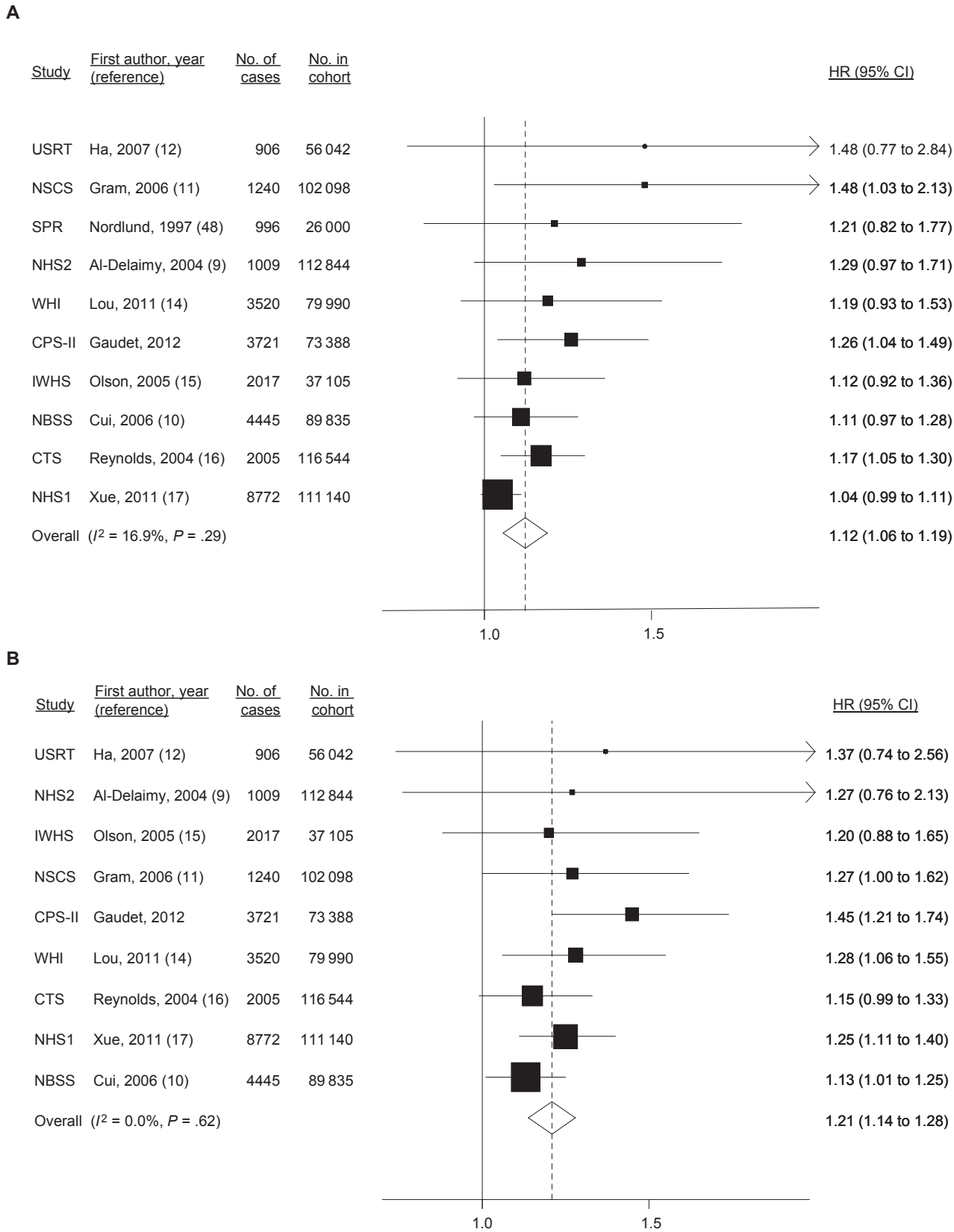

Figure 2. Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of breast cancer associated with younger age at smoking initiation (**A**) and smoking initiation before first birth (**B**) of published cohort studies. Studies are referred to by study abbreviation (defined in Supplementary Table 1, available online), first author, year of publication, sample size of case patients and cohort, and category of comparison and weighted and ranked according to the inverse of the variance of the log hazard ratio estimate. The hazard ratios are represented by the **squares** (the size is proportional to the weights used in the meta-analysis) and the confidence intervals are represented by the **error bars**. The **solid vertical line** represents the null value, and the **dotted vertical line** represents the overall summary estimate.

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