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Active and passive cigarette smoking and breast cancer risk: Results from the EPIC cohort

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Abbreviations: BMI: body mass index; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; ER: estrogen receptor; FFTP: first full-term pregnancy; HR: hazard ratio; IARC: International Agency for Research on Cancer; MHT: menopausal hormone therapy; OC: oral contraceptive; PAH: polycyclic hydrocarbons; PR: progesterone receptor

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Recent cohort studies suggest that increased breast cancer risks were associated with longer smoking duration, higher pack-years and a dose-response relationship with increasing pack-years of smoking between menarche and first full-term pregnancy (FFTP). Studies with comprehensive quantitative life-time measures of passive smoking suggest an association between passive smoking dose and breast cancer risk. We conducted a study within the European Prospective Investigation into Cancer and Nutrition to examine the association between passive and active smoking and risk of invasive breast cancer and possible effect modification by known breast cancer risk factors. Among the 322,988 women eligible for the study, 9,822 developed breast cancer (183,608 women with passive smoking information including 6,264 cases). When compared to women who never smoked and were not being exposed to passive smoking at home or work at the time of study registration, current, former and currently exposed passive smokers were at increased risk of breast cancer (hazard ratios (HR) [95% confidence interval (CI)] 1.16 [1.05–1.28], 1.14 [1.04–1.25] and 1.10 [1.01–1.20], respectively). Analyses exploring associations in different periods of life showed the most important increase in risk with pack-years from menarche to FFTP (1.73 [1.29–2.32] for every increase of 20 pack-years) while pack-years smoked after menopause were associated with a significant decrease in breast cancer risk (HR = 0.53, 95% CI: 0.34–0.82 for every increase of 20 pack-years). Our results provide an important replication, in the largest cohort to date, that smoking (passively or actively) increases breast cancer risk and that smoking between menarche and FFTP is particularly deleterious.

What's new?

The EPIC study is the largest cohort analysis on smoking and breast cancer to date. In this analysis of data from that study, the authors have confirmed that both active and passive exposure to cigarette smoke increases breast cancer risk. These results emphasize that it's important to distinguish between passive exposure and no exposure when analyzing the relationship between smoking and breast cancer. The authors also confirm that the most potent window of exposure for smoking and breast cancer risk is between menarche and first full term pregnancy.

Tobacco smoking is among the leading preventable risk factors for a variety of diseases.[1] The biological plausibility of an association with breast cancer risk has been long suggested because carcinogens found in tobacco smoke may pass into the blood stream and be transported to the breast.[2]

Most epidemiological studies concluded to a weak positive association and suggested that there may be an increased risk with heavy smoking, smoking of long duration, smoking before a first full-term pregnancy (FFTP) and passive smoking.[3–11] A number of reports also raised the hypothesis that this increase may be stronger in women with high levels of estrogens.[12,13] Previously published reviews of the literature that included measures of passive smoking concluded that passive smokers (and particularly premenopausal women) may be at increased risk of developing breast cancer when compared to women never regularly exposed to tobacco smoke in any form.[4,14–17] In 2000, Morabia *et al.* demonstrated that separating passive smokers from never exposed had a major impact on associations observed for active smokers.[18] Since then, studies that included comprehensive measures of lifetime occupational and residential passive smoking consistently observed an increased risk, whereas studies with less comprehensive measures saw no effect or a much weaker effect.[4,7,14,16,17] However, a recent meta-analysis showed an increased breast cancer risk for passive smokers in retrospectively collected data but not in prospectively collected data,[19] possibly because of poorer assessment of lifetime passive smoking exposure in prospective cohort studies. In addition, two recent large cohort studies showed that the increase in breast cancer risk with active smoking is concentrated in the period between menarche and first pregnancy, following a dose-response relationship with pack-years, and observed a reduced risk after first pregnancy or after menopause.[7,11,20]

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a multicenter prospective study initiated in 1992 in ten European countries.[21] With close to 10,000 breast cancer cases (including over 6,000 cases in the population with available data on passive smoking) EPIC offers a unique opportunity to examine in depth whether, after account of passive exposure at recruitment, smoking affects breast cancer risk differently (*i*) in current, former and passive smokers, (*ii*) in different periods of a woman's life, (*iii*) in different subgroups exposed to specific breast cancer risk factors, in particular according to menopausal status, hormone receptor status of the tumor, to BMI and to alcohol intake.

Material and Methods

Study population

Eligible study subjects were from the general population residing in a given geographical area, *i.e.*, a town or a province. There were, however, a few exceptions as follows: the French cohort was based on members of a health insurance plan covering state school employees; the Italian and Spanish cohorts included members of local blood donor associations; the Utrecht and Florence cohorts were based on women attending breast cancer screening and part of the Oxford cohort consisted of vegetarians and healthy eaters. Eligible subjects were invited by mail to participate in the study. In some cases (*e.g.*, blood donors) the first invitation was by personal contact. Those who accepted signed an informed consent and completed questionnaires on their diet, lifestyle and medical history. The study was approved by the IARC Ethical Review Committee and by the Ethical Committees of the participating centers.

From the initial pool of 367,903 subjects, we excluded women who reported a history of cancer ($N = 19{,}853$), women with incomplete follow-up data ($N = 3{,}862$), women with no information on smoking status ($N = 8{,}687$) and women from the Swedish centre Umea ($N = 12{,}513$) where data on reproductive factors were not available. This left 322,988 women originating from Denmark (29,262), France (64,864), Germany (27,843), Greece (14,617), Italy (31,111), The Netherlands (26,848), Norway (33,856), Spain (25,343), Sweden (14,394) and the United Kingdom (54,850).

Data collection

Data were collected on a large number of lifestyle and health factors that are of interest in studies on nutrition and cancer because they may be related to nutritional status or may be known or suspected cancer risk factors. A common set of questions was agreed on and translated into national questionnaires, including those addressing cigarette smoking status (current, former and never), amount and duration of cigarettes smoked and age at initiation. Information on smoking habits was not updated after baseline; therefore, duration among current smokers refers to duration between initiation and recruitment into the study (from 1992 in France until 2000 in Norway). Daily number of cigarettes usually smoked was requested for current smokers. Information on the number of cigarettes smoked per day over an individual's lifetime was also collected (except in France and Sweden, and these countries were therefore excluded from analyses on this variable and from analyses on pack-years at different periods of life, $N = 79{,}258$). Age at initiation was recorded as a categorical variable in two countries (France and Norway) and as a continuous variable elsewhere. Questions on passive smoking were asked in 16 centers, from seven countries (France, Italy, The Netherlands, Germany, Denmark, Sweden and Norway) corresponding to 183,608 women. Information was collected on adult residential exposure and adult occupational exposure (except in France, whose cohort population is mainly composed of teachers). The following question was asked about adult passive smoking exposure: "Does someone regularly smoke in your presence at home/work?" In three countries [France, Italy (except Naples) and Denmark], childhood exposure from parents was also registered and taken into account, so that in other countries, women defined as never exposed to tobacco may include subjects with passive childhood exposure to tobacco smoke. The following questions were asked about childhood smoking exposure: "Did any of your parents smoke when you grew up?" or "When you were a child, did you spend time where smoking was present." Questions about passive smoking intensity (time spent around smokers and number of cigarettes smoked by the partner) were only asked in France and Italy and were therefore not considered in this analysis.

As only menopausal status at baseline was recorded, further classification of women who were premenopausal at baseline was based on age, considering as premenopausal a woman until age 50, and as postmenopausal a woman after age 55. Thus, women who were premenopausal at baseline contributed to the premenopausal group for the period between enrolment and age 50, and to the post-menopausal group from age 55 until the end of follow-up. Premenopausal women at baseline did not contribute person-years while aged between age 50 and 55.

Follow-up and ascertainment of breast cancer

Incident breast cancer cases were identified through population cancer registries (Denmark, Italy, The Netherlands, Spain, UK and Norway) or active follow-up (France, Germany and Greece), depending on the follow-up procedures in each of the participating countries. Active follow-up used a combination of methods including active follow-up through participants and their next-of-kin, and use of health insurance records and existing pathology registries. Mortality data were also obtained at the regional or national level. The 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) was used to classify mortality and cancer incidence data and ICD-O-3 to define breast tumor. In our analysis, women were followed

from study entry (1992–2000) until first breast cancer diagnosis, death or last known date of contact (between 2005 and 2010 depending on the center).

Overall, among the 322,988 women followed for a mean duration of 11 years, 9,822 first invasive breast cancer cases occurred. When passive smoking was considered, the population was restricted to 183,608 women, with 6,264 cases.

Statistical analysis

Hazard ratio (HR) and 95% confidence intervals (CIs) were used as the measures of association between smoking and breast cancer and were estimated using Cox proportional hazard regression models with age as time scale, and stratified by study center. Separate analyses were performed taking into account or not information on passive smoking and the category of women never exposed to active (or passive) smoking was used as reference in all analyses. Adjustments were performed for the following variables, recorded at baseline: educational level (none or primary, professional, secondary, university, missing), body mass index (BMI; $>$18.5, 18.5–24, 25–29, $\geq$30 kg/m^2), daily alcohol consumption (0, 0–10, $>$10 g/day, missing), age at menarche ($<$12, 12, 13, $>$13 years, never/missing), parity and age at FFTP (nulliparous, parous and age at FFTP $<$ 25, parous and age at FFTP $\geq$ 25, missing), menopausal status (premenopausal, perimenopausal, postmenopausal), use of oral contraceptives (OC; ever, never, missing) and menopause hormone therapy (MHT; ever, never, missing). Crude and adjusted HR were of similar magnitude, and we chose to present only adjusted HR. Trends were tested using ordered continuous variables, after exclusion of never smokers and of women with missing values. Risk of breast cancer was also analyzed according to menopausal status (premenopausal, postmenopausal never MHT users, postmenopausal ever MHT users), breast tumor subtypes (ER+/PR+; ER+/PR−; ER−/PR+; ER−/PR−), BMI (lean: $<$25 kg/m^2; overweight: $\geq$ 25 kg/m^2), alcohol consumption (nondrinkers; 1–9 g/day; $\geq$10 g/day), parity (nulliparous; parous), OC use (never users; ever users) and educational level (none or primary and professional; secondary and university). For each of these variables, heterogeneity between groups was tested by adding a multiplicative interaction term to the model and by using likelihood ratio tests for interactions.

Results

Characteristics of the smoking habits by EPIC country are shown in Table 1. Overall, 56.7% of the study population had never smoked, 23.3% were former smokers and 20.0% were current smokers at baseline. Smoking was more frequent in Northern cohorts (Norway, Denmark and The Netherlands) than in Southern cohorts (Greece, Spain and France). UK, Germany and Italy had intermediate rates of smokers. Smoking initiation was particularly early in The Netherlands, and late in Greece. Among current smokers at baseline, cohorts in Denmark, The Netherlands and Greece had the highest prevalence of heavy smokers, cohorts in Norway, UK and France the lowest. Out of the 183,608 women with information on passive smoking, 14.2% were not being exposed to tobacco smoke (neither at work nor at home at recruitment into the cohort), 42.6% had only been passively exposed, 7.1% were former or current active smokers never exposed to passive smoking and 36.1% were both active smokers and exposed to passive smoking.

Table 2 presents the distribution of breast cancer risk factors according to smoking status. Smoking was more frequent among the youngest EPIC women, who were more often current than former smokers. Women with the highest educational level were more often former or never smokers. Compared to never smokers, ever smokers were leaner, had higher intake of alcohol, were younger at first pregnancy, were more often premenopausal and were more often users of MHT.

Table 3 presents breast cancer risks associated with smoking, in the whole EPIC population (reference never exposed to active smoking), and in the data set restricted to centers with information on passive smoking (reference never exposed to active smoking or not exposed to passive smoke in their childhood—for centers that collected this information—nor living with a smoker nor being exposed at work at recruitment into the cohort). In the whole study population, the adjusted HR was similar for current (HR = 1.06, 95% CI: 1.00–1.12) and former (HR = 1.05, 95% CI: 1.00–1.10) active smokers compared to never active smokers. In centers where data on passive smoking were available, the adjusted HR for passive smoking (HR = 1.10, 95%: 1.01–1.20) was very similar to that for former and current smoking (HR = 1.14, 95% CI: 1.04–1.25 and HR = 1.16, 95% CI: 1.05–1.28, respectively). In current smokers who did not report any passive smoking exposure the HR was 1.33 (95% CI: 1.09–1.62). Among women exposed to passive smoking, those exposed to passive smoking at home only had the highest risk of developing breast cancer (HR = 1.30, 95%: 1.07–1.59).

Generally, stronger associations were observed when women exposed to passive smoking were excluded from the reference category. We observed no clear trend of risk over categories of duration of smoking or duration since smoking cessation among former smokers. In current smokers, however, a significant trend was observed with longer duration of smoking with a 20% higher risk for a smoking duration of more than 30 years compared to never exposed to active or passive smoking (HR = 1.19, 95% CI: 1.06–1.33, p_{trend} = 0.0214), whereas no increase in risk was observed for current smokers during less or equal to 20 years compared to never exposed (HR = 0.82, 95% CI: 0.50–1.35 for smoking duration 0–10 years and HR = 0.93, 95% CI: 0.72–1.20 for smoking duration 11–20 years). Current smokers who smoked more than 20 pack-years had a risk of 1.34 (95% CI: 1.14–1.58) compared to never exposed. Although overall, age at smoking initiation was not associated with breast cancer risk, current smokers who started smoking before their first

Table 1. Smoking characteristics of the study population (n = 322,988), by country (%), EPIC cohort 1992–2000

	All women	France	Italy	Spain	UK	Netherlands	Greece	Germany	Sweden	Denmark	Norway
Smoking status											
n	322,988	64,864	31,111	25,343	54,850	26,848	14,617	27,843	14,394	29,262	33,856
Never	56.7	70.6	53.6	71.3	60.8	40.8	76.4	56.0	45.6	43.7	35.6
Former	23.3	20.2	20.1	9.9	28.1	31.3	5.7	25.6	27.7	24.6	30.8
Current	20.0	9.2	26.2	18.8	11.1	27.9	17.9	18.4	26.7	31.7	33.6
Smoking status among women with data on passive smoking											
n	183,608	61,692	19,627	0	0	11,578	0	14,700	12,912	29,243	33,856
Not exposed to passive smoking at home or at work at time of cohort recruitment[1]	14.2	12.0	12.6	0.0	0.0	23.0	0.0	50.4	8.0	2.4	12.8
Passive exposure only[2]	42.6	58.7	72.3	0.0	0.0	14.8	0.0	10.1	37.0	41.3	22.8
Former active smoker, not exposed to passive smoking at home or at work at time of cohort recruitment[1]	5.0	2.1	0.6	0.0	0.0	16.1	0.0	18.3	3.0	1.0	7.4
Current active smoker, not exposed to passive smoking at home or at work at time of cohort recruitment[1]	2.1	0.6	0.9	0.0	0.0	2.7	0.0	8.7	2.1	0.2	4.4
Former active smoker also exposed to passive smoking[2]	17.5	18.2	4.2	0.0	0.0	11.0	0.0	4.8	25.0	23.7	23.4
Current active smoker also exposed to passive smoking[2]	18.6	8.4	9.4	0.0	0.0	32.4	0.0	7.7	24.9	31.4	29.2
Smoking initiation among former smokers (years)											
n	75,282	13,121	6,264	2,498	15,419	8,391	830	7,117	3,990	7,214	10,438
<16	10.7	3.5	13.3	16.1	15.2	18.8	5.4	9.7	9.4	13.0	3.5
16–26	73.4	67.2	71.6	69.1	71.9	72.0	69.2	81.2	59.6	75.9	85.6
≥26	10.5	13.1	15.0	13.4	5.4	6.5	20.9	9.0	28.4	10.5	7.9
Missing	5.4	16.2	0.1	1.4	7.5	2.7	4.5	0.1	2.6	0.6	3.0
Smoking initiation among current smokers (years)											
n	64,629	5,948	8,163	4,764	6,066	7,491	2,611	5,119	3,837	9,267	11,363
<16	12.4	4.1	14.3	12.9	18.9	24.5	5.4	10.5	8.3	14.2	6.2
16–26	71.2	64.7	66.5	67.0	66.8	66.2	70.0	77.5	54.2	73.6	86.4
≥26	14.5	25.3	18.7	18.9	5.7	8.3	23.9	11.9	35.1	11.5	7.3
Missing	1.9	5.9	0.5	1.2	8.6	1.0	0.7	0.1	2.4	0.7	0.1
Smoking initiation in relation with age at full-term pregnancy among ex-smokers (years)[3]											
n	64,137	11,879	5,341	2,158	11,742	6,950	674	5,972	3,495	6,311	9,597
Before	80.6	66.1	83.8	82.0	83.4	88.1	68.7	85.5	65.1	83.3	89.4

Table 1. Smoking characteristics of the study population (n = 322,988), by country (%), EPIC cohort 1992–2000 (Continued)

	All women	France	Italy	Spain	UK	Netherlands	Greece	Germany	Sweden	Denmark	Norway
After	11.6	9.8	16.0	15.6	6.8	7.8	25.7	14.2	30.3	15.2	7.6
Missing	7.8	24.1	0.2	2.4	9.8	4.1	5.6	0.3	4.6	1.5	3.0
Smoking initiation in relation with age at full-term pregnancy among current smokers (years)[3]											
n	54,414	5,350	6,917	4,089	3,997	5,746	2,180	4,225	3,360	8,153	10,397
Before	77.2	63.1	78.0	73.5	78.3	83.7	64.4	78.2	53.7	78.1	90.6
After	18.7	20.8	21.4	24.0	9.5	11.6	33.2	21.3	42.3	19.1	9.3
Missing	4.1	16.1	0.6	2.5	12.2	4.7	2.4	0.5	4.0	2.8	0.1
Duration of smoking among former smokers (years)											
n	75,282	13,121	6,264	2,498	15,419	8,391	830	7,117	3,990	7,214	10,438
0–10	32.5	24.8	28.3	35.2	34.7	27.1	32.5	43.1	36.5	25.0	41.6
10–20	29.8	28.8	37.5	42.8	28.4	29.8	35.9	32.1	30.4	23.7	27.6
20–30	19.8	19.4	25.4	18.0	15.4	23.1	19.8	14.7	19.7	21.9	23.5
>30	9.8	6.7	8.5	2.4	10.6	15.9	7.1	5.9	10.9	22.2	3.4
Missing	8.1	20.3	0.3	1.6	10.9	4.1	4.7	4.2	2.5	7.2	3.9
Duration of smoking among current smokers (years)											
n	64,629	5,948	8,163	4,764	6,066	7,491	10	5,119	3,837	9,267	11,363
0–10	4.1	1.7	2.2	6.1	12.5	6.7	9.8	1.9	4.8	1.0	1.4
10–20	13.3	10.9	13.8	32.1	18.6	13.7	43.4	19.3	10.4	2.5	3.5
20–30	36.0	39.5	45.2	53.7	22.4	24.3	34.6	50.5	28.7	10.4	52.1
>30	44.7	42.0	38.3	6.9	37.9	54.3	11.5	28.2	53.6	85.4	42.8
Missing	1.9	5.9	0.5	1.2	8.6	1.0	0.7	0.1	2.5	0.7	0.2
Cigarettes per day among current smokers											
n	64,629	5,948	8,163	4,764	6,066	7,491	2,611	5,119	3,837	9,267	11,363
1–15	53.8	52.9	57.7	54.6	52.4	44.8	46.5	58.1	50.6	47.5	64.0
≥15	42.4	34.0	42.2	44.5	39.6	49.4	53.2	41.6	44.8	51.8	32.2
Missing	3.8	13.1	0.1	0.9	8.0	5.8	0.3	0.3	4.6	0.7	3.8
Lifetime cigarettes per day among former smokers											
n	75,282	13,121	6,264	2,498	15,419	8,391	830	7,117	3,990	7,214	10,438
<6	20.8	0.0	24.5	34.6	22.1	31.9	24.5	31.5	0.0	27.6	25.9
6–10	9.7	0.0	26.7	14.0	8.7	12.7	13.3	13.4	0.0	15.0	6.9
10–15	18.5	0.0	17.1	18.4	21.4	17.3	21.9	16.6	0.0	24.1	44.1
≥15	16.8	0.0	15.2	28.2	29.6	27.5	33.0	17.3	0.0	20.7	10.7
Missing	34.2	100.0	16.5	4.8	18.2	10.6	7.3	21.2	100.0	12.6	12.4

Table 1. Smoking characteristics of the study population (n = 322,988), by country (%), EPIC cohort 1992–2000 (Continued)

	All women	France	Italy	Spain	UK	Netherlands	Greece	Germany	Sweden	Denmark	Norway
Lifetime cigarettes per day among current smokers											
n	64,629	5,948	8,163	4,764	6,066	7,491	2,611	2,119	3,837	9,267	11,363
<6	14.3	0.0	22.3	27.8	15.3	15.9	23.2	26.0	0.0	11.5	8.6
6–10	18.6	0.0	19.9	23.2	16.5	17.0	18.5	25.0	0.0	20.3	29.3
10–15	24.1	0.0	19.2	23.9	26.4	25.6	24.4	25.5	0.0	35.5	36.5
≥15	22.0	0.0	14.0	23.9	30.3	34.2	32.9	22.9	0.0	30.7	23.6
Missing	21.0	100.0	24.6	1.2	11.5	7.3	1.0	0.6	100.0	2.0	2.0
Lifetime amount of pack-years among former smokers											
n	75,282	0	6,264	2,498	15,419	8,391	830	7,117	0	7,214	10,438
1–5	27.2	0.0	37.7	42.6	28.8	33.6	32.3	37.0	0.0	29.0	45.9
5–10	15.3	0.0	20.0	20.7	19.8	18.1	23.9	19.5	0.0	19.3	20.9
10–15	9.4	0.0	12.2	13.2	12.1	12.3	13.5	10.1	0.0	12.6	12.9
15–20	5.7	0.0	6.1	8.8	8.5	8.5	7.7	6.0	0.0	9.8	4.5
≥20	8.0	0.0	7.5	9.9	12.6	16.9	15.3	6.2	0.0	16.7	3.4
Missing	34.2	0.0	16.5	4.8	18.2	10.6	7.3	21.2	0.0	12.6	12.4
Lifetime amount of pack-years among current smokers											
n	64,629	0	8,163	4,764	6,066	7,491	2,611	5,119	0	9,267	11,363
1–5	10.1	0.0	13.6	23.3	17.1	11.0	23.2	16.6	0.0	4.3	5.5
5–10	12.8	0.0	17.7	26.5	13.9	13.9	24.2	23.1	0.0	7.8	9.9
10–15	15.5	0.0	15.6	20.2	12.2	13.8	18.4	21.2	0.0	11.3	29.9
15–20	14.1	0.0	11.7	13.6	12.6	14.3	13.4	15.6	0.0	16.4	26.6
≥20	26.5	0.0	16.8	15.1	32.7	39.7	19.7	22.9	0.0	58.2	26.2
Missing	21.0	0.0	24.6	1.3	11.5	7.3	1.1	0.6	0.0	2.0	2.0

[1]Women not exposed to passive smoke in their childhood (for centers that collected this information) nor living with a smoker nor being exposed at work at recruitment into the cohort.
[2]Women exposed to passive smoke either during their childhood (for centers that collected this information) or living with a smoker, or exposed at work at recruitment into the cohort, or all of these.
[3]Only for parous women.

Table 2. Characteristics of the study population (n = 322,988) according to smoking status at inclusion (%), EPIC cohort 1992–2000

	Never (n = 183,077)	Former (n = 75,282)	Current (n = 64,629)
Birth cohort			
<1931	9.7	8.4	4.0
1931–1935	13.3	10.9	8.5
1936–1940	17.5	13.8	13.1
1941–1945	20.0	20.1	21.0
1946–1950	18.7	21.5	20.3
1951–1955	8.5	12.5	15.6
1956–1960	5.7	8.3	11.3
>1960	6.5	4.5	6.2
Educational level			
None or primary	28.8	18.4	28.2
Professional	18.2	25.8	28.4
Secondary	25.9	25.3	23.7
University	22.5	25.5	17.3
Missing	4.6	5.0	2.4
BMI (kg/m^2)			
<18.5	2.0	1.5	2.6
18.5–25	54.1	57.4	59.6
25–30	29.3	29.6	27.9
≥30	14.6	11.5	9.9
Physical activity			
Inactive	24.8	16.7	20.3
Moderately inactive	33.3	30.3	28.3
Moderately active	21.7	22.1	17.8
Active	12.8	16.0	14.5
Missing	7.3	14.9	19.1
Alcohol consumption (g ethanol per day)			
0	19.6	10.6	15.4
0–10	55.5	55.5	50.8
>10	24.2	32.8	33.1
Missing	0.7	1.1	0.7
Age at menarche			
<12	14.8	14.7	15.6
12	21.5	20.5	20.8
13	25.6	25.9	25.0
>13	36.9	37.6	37.3
Never/Missing	1.2	1.3	1.3
Parity and age at first full-term pregnancy (FFTP)			
Nulliparous	15.2	14.7	15.7
Parous and age at FFTP < 25	41.7	40.1	49.4
Parous and age at FFTP ≥ 25	40.8	43.0	33.0
Missing	2.3	2.2	1.9
Ever use of oral contraceptives			
No	47.4	32.8	33.9
Yes	52.1	66.7	65.6
Missing	0.5	0.5	0.5
Menopausal status			
Premenopausal	32.8	34.7	38.9
Perimenopausal	17.4	20.5	19.5
Postmenopausal	49.8	44.8	41.6
Ever use of menopausal hormone therapy			
No	71.9	66.8	68.7
Yes	23.5	27.4	25.5
Missing	4.6	5.8	5.8

pregnancy seemed to have a higher BC risk (HR = 1.21, 95% CI: 1.08–1.36) than those who started smoking after their first pregnancy (HR = 1.05, 95% CI: 0.88–1.24) ($p_{heterogeneity}$ = 0.15). Similarly, ever smokers who started smoking before their FFTP had a higher risk (HR = 1.15, 95% CI: 1.04–1.27) compared to those who stated smoking after FFTP (HR = 1.07, 95% CI: 0.93–1.22) ($p_{heterogeneity}$ = 0.15). Analyses exploring associations of breast cancer with pack-years relevant to different periods of life showed a significant increase of risk with pack-years from menarche to before first birth (HR = 1.71, 95% CI: 1.12–2.59 for every increase of 20 pack-years), while pack-years smoked after menopause were associated with a significant decrease in breast cancer risk (HR = 0.53, 95% CI: 0.34–0.82 for every increase of 20 pack-years) (Table 4). The decrease in breast cancer risk after menopause with increasing pack-years was observed among women whether they used MHT or not, although statistical significance was reached only among non-MHT users, possibly because of lower numbers in the group using MHT.

Results stratified by the main breast cancer risk factors and tumor types are presented in Figures 1 and 2. Although none of the interaction test was statistically significant, some differences in the magnitude of the associations could be noted in some specific subgroups. Menopausal status only affected current smokers, with an indication of a stronger association in premenopausal (HR = 1.32, 95% CI: 0.98–1.77) than in postmenopausal women (HR = 1.10, 95% CI: 0.92–1.31 and HR = 1.15, 95% CI: 0.97–1.36 for never and ever MHT users, respectively). Adjustment for age at menopause further attenuated the estimates for current smokers *vs.* never exposed among never MHT users (HR: 1.02, 95% CI: 0.92–1.30). Risk associated with current smoking was statistically significant (or close to) for ER+ (HR = 1.23, 95% CI: 1.04–1.45 for ER+/PR+ and HR = 1.34, 95% CI: 0.99–1.82

for ER+/PR−) but not for ER− tumors (HR = 0.69, 95% CI: 0.31–1.57 for ER−/PR+ and HR = 1.13, 95% CI: 0.83–1.54 for ER−/PR−, $p_{heterogeneity} > 0.4841$). Stratification by BMI resulted in stronger associations among leaner compared to overweight women for premenopausal passive (HR = 1.19, 95% CI: 0.86–1.64) and former smokers (HR = 1.19, 95% CI: 0.83–1.66) and postmenopausal former smokers (HR = 1.20, 95% CI: 1.04–1.38). When stratifying by alcohol consumption levels, increased risk of breast cancer associated with passive, former or current smoking seemed to be restricted to nondrinkers (HR = 1.25, 95% CI: 1.01–1.55, HR = 1.42, 95% CI: 1.10–1.83 and HR = 1.33, 95% CI: 1.02–1.73, respectively). Apparently stronger associations were also observed among OC never users compared to ever users, especially for former (HR = 1.22, 95% CI: 1.05–1.41) and current smokers (HR = 1.33, 95% CI: 1.14–1.56) and for current and passive smokers with low (HR = 1.21, 95% CI: 1.04–1.41 and HR = 1.18, 95% CI: 1.02–1.37 for current and passive smokers, respectively) compared to high educational level (HR = 1.12, 95% CI: 0.98–1.28 and HR = 1.05, 95% CI: 0.94–1.17). No significant heterogeneity was observed by EPIC country.

No significant heterogeneity was observed across subgroups for associations between pack-years smoked in different periods of life and breast cancer risk (Fig. 2).

Discussion

Our results are consistent with an increase in breast cancer risk related to smoking, not only in former or current active smokers but also in passive smokers. This increase was most apparent in women who smoked between menarche and FFTP. In postmenopause, smokers seemed to be at decreased risk of breast cancer.

Major strengths of our study are its large size and its ability to explore associations in various subgroups as well as the availability of data on passive smoking. Excluding passive smokers from the reference category is especially important when the risks associated with passive and active smoking are of similar magnitude. Also, passive smoking is important to consider separately, because a high proportion of women, especially in the older age groups, have been exposed to passive smoking. Further strengths of this large multicenter study include its size, and its large variation in tobacco exposure because the different countries are at different stages of the tobacco epidemic, though—due to a healthy participant effect—the proportion of smokers (current and, to a lesser extent, former smokers) was rather low. Women of the EPIC study who smoke have characteristics similar to those described in former studies[9,22] being, as compared to never smokers, leaner, more often alcohol and oral contraceptives users, younger at first pregnancy and less educated (with the exception of those who had never been at school and who may avoid smoking for economic reasons). These characteristics are unlikely to account for our results as they were adjusted for and as none was an effect modifier. One particularity of the EPIC study is its larger proportion, compared to other Western cohorts, of lean women (56.1% with BMI < 25 kg/m^2), which gives the unique opportunity to evaluate risk factors that could be masked by obesity. A limitation of our study, and of most cohort studies published on that topic, is its inability to update information on smoking habits. Misclassification of exposure is likely to affect more specifically current smokers than former or never smokers, because at the age of the EPIC participants, women are more likely to quit smoking than to initiate smoking or smoke again and therefore is likely to have resulted in an overestimation of smoking duration. Although not related to the outcome, owing to the prospective design of the study, such misclassification would most likely have diluted the magnitude of the relationships in current smokers and would likely only attenuate relative risk estimates. Another major limitation was that the passive smoking measures did not allow for quantitative/dose-response analyses of passive smoking. In addition, only three countries out of the ten participating in EPIC asked questions about passive smoking exposure during childhood and questions about passive exposure in adulthood were limited to the time of recruitment into the study. As the comprehensiveness of the passive smoking measures has been shown to have a major impact on the magnitude of the passive smoking effect observed,[4,7,8,14,17] the measures of passive smoking exposure available in the EPIC cohort are likely to have underestimated risk associated with passive exposure and might also have diluted the active smoking risks, if some passive smokers were incorrectly classified as "unexposed." Indeed, cohort studies with better passive smoking exposure measure observed higher risk estimates in the most passively exposed women[8,23] and higher risks were also observed in premenopausal women than in postmenopausal women in studies where lifetime exposure to passive smoking was considered.[4] In the EPIC study, the evaluation of the risk in premenopausal women was limited by the small number of cases in this subgroup.

Furthermore, in EPIC, as in most existing cohorts, the selection of subjects due to a "healthy participant effect" results in a low percentage of smokers and in smokers potentially adopting healthy behaviors so as to counterbalance smoking, making it more difficult to detect associations. We took into account a number of covariates, including body weight, which is causally affected by smoking. However, a minimally adjusted model with age only as covariate resulted in HRs materially unchanged from the heavily modeled HRs, showing no important effect of any adjustment. Age at menopause was not included as a covariate as it was considered to be a possible intermediate factor in the relationship between smoking and breast cancer risk.[24] Potential confounders of the smoking and breast cancer association, such as vitamin supplementation or frequency of mammography, were not recorded in all centers, and could therefore not be adjusted for. This, and the fact that we were not able to adjust for changes during follow-up of established risk factors

Table 3. Adjusted HRs of breast cancer in relation to cigarette smoking among all women (n = 322,988) and among women with data on passive smoking (n = 183,608), EPIC cohort 1992–2000

All women (n = 322,988)			Women with data on passive smoking (n = 183,608)		
	Cases	HR[1] (95% CI)		Cases	HR[1] (95% CI)
Never exposed to active smoking	5,421	Reference	Never exposed to active smoking and not exposed to passive smoking at home or at work at time of cohort recruitment[2]	725	Reference
Smoking status					
Ever exposed to active smoking	4,401	1.06 (1.01–1.10)	Ever exposed to active or passive smoking[3]	5,539	1.12 (1.03–1.22)
			Passive exposure[3]	2,872	1.10 (1.01–1.20)
			Passive exposure in childhood only	811	1.01 (0.90–1.12)
			Passive exposure at home only	119	1.30 (1.07–1.59)
			Passive exposure at work only	392	1.08 (0.95–1.23)
			Passive exposure in childhood and at home	156	0.95 (0.79–1.13)
			Passive exposure in childhood and at work	718	1.07 (0.95–1.19)
			Passive exposure at home and at work	107	1.08 (0.87–1.32)
			Passive exposure in childhood, at home and at work	258	1.04 (0.90–1.21)
Former exposure	2,495	1.05 (1.00–1.10)	Former active exposure	1,441	1.14 (1.04–1.25)
			Not exposed to passive smoking at home or at work at time of cohort recruitment[2]	251	1.11 (0.96–1.29)
			Also exposed to passive smoking[3]	1,190	1.14 (1.03–1.26)
Current exposure	1,906	1.06 (1.00–1.12)	Current active exposure	1,226	1.16 (1.05–1.28)
			Not exposed to passive smoking at home or at work at time of cohort recruitment[2]	116	1.33 (1.09–1.62)
			Also exposed to passive smoking[3]	1,110	1.14 (1.03–1.27)
Duration of smoking among former smokers (years)					
0–10	752	1.10 (1.01–1.18)	0–10	465	1.24 (1.10–1.40)
10–20	680	0.98 (0.91–1.07)	10–20	369	1.04 (0.91–1.18)
20–30	553	1.09 (0.99–1.19)	20–30	301	1.10 (0.96–1.27)
>30	272	0.99 (0.87–1.12)	>30	140	1.01 (0.83–1.21)
p trend[4]		0.9699	p trend[4]		0.4977
Duration of smoking among current smokers (years)					
0–10	35	0.94 (0.68–1.32)	0–10	16	0.82 (0.50–1.35)
10–20	146	0.95 (0.81–1.13)	10–20	66	0.93 (0.72–1.20)
20–30	582	1.03 (0.94–1.13)	20–30	370	1.19 (1.04–1.36)
>30	1,103	1.09 (1.02–1.17)	>30	751	1.19 (1.06–1.33)
p trend[4]		0.0460	p trend[4]		0.0214
Years since cessation of smoking among former smokers					
Current	1,906	Reference	Current	1,226	Reference
0–10	785	0.97 (0.89–1.05)	0–10	458	0.95 (0.85–1.06)
10–20	750	0.96 (0.88–1.05)	10–20	404	0.91 (0.81–1.02)
>20	861	1.02 (0.94–1.11)	>20	517	1.07 (0.96–1.19)
p trend[4]		0.1451	p trend[4]		0.0779

Table 3. Adjusted HRs of breast cancer in relation to cigarette smoking among all women (n = 322,988) and among women with data on passive smoking (n = 183,608), EPIC cohort 1992–2000 (Continued)

All women (n = 322,988)			Women with data on passive smoking (n = 183,608)		
	Cases	HR[1] (95% CI)		Cases	HR[1] (95% CI)
Cigarette per day among current smokers					
1–15	988	1.02 (0.95–1.10)	1–15	634	1.13 (1.01–1.27)
≥15	853	1.12 (1.03–1.20)	≥15	543	1.23 (1.09–1.39)
p trend[4]		0.1894	p trend[4]		0.3665
Lifetime cigarette per day among former smokers					
<6	449	0.94 (0.85–1.04)	<6	185	1.04 (0.86–1.24)
6–10	230	0.98 (0.86–1.13)	6–10	73	0.98 (0.76–1.27)
10–15	424	1.07 (0.96–1.18)	10–15	210	1.14 (0.95–1.36)
≥15	398	1.13 (1.01–1.26)	≥15	141	1.23 (1.00–1.50)
p trend[4]		0.0068	p trend[4]		0.1122
Lifetime cigarette per day among current smokers					
<6	235	0.99 (0.87–1.13)	<6	97	1.19 (0.94–1.49)
6–10	318	1.03 (0.91–1.16)	6–10	176	1.14 (0.94–1.38)
10–15	459	1.11 (1.00–1.23)	10–15	289	1.32 (1.11–1.56)
≥15	403	1.09 (0.97–1.21)	≥15	236	1.27 (1.07–1.52)
p trend[4]		0.2624	p trend[4]		0.3700
Lifetime amount of pack–years among former smokers					
1–5	563	0.97 (0.89–1.07)	1–5	250	1.09 (0.92–1.29)
5–10	327	0.98 (0.87–1.10)	5–10	135	1.07 (0.87–1.31)
10–15	235	1.13 (0.99–1.29)	10–15	87	1.11 (0.88–1.42)
15–20	145	1.07 (0.91–1.23)	15–20	55	1.17 (0.87–1.56)
≥20	231	1.11 (0.97–1.27)	≥20	82	1.12 (0.88–1.44)
p trend[4]		0.045	p trend[4]		0.8143
Lifetime amount of pack-years among current smokers					
1–5	129	1.01 (0.85–1.21)	1–5	42	1.08 (0.78–1.49)
5–10	193	1.06 (0.91–1.23)	5–10	86	1.30 (1.02–1.65)
10–15	227	0.96 (0.84–1.10)	10–15	127	1.08 (0.88–1.34)
15–20	265	1.08 (0.95–1.22)	15–20	161	1.22 (1.00–1.48)
≥20	601	1.11 (1.02–1.22)	≥20	382	1.34 (1.14–1.58)
p trend[4]		0.1212	p trend[4]		0.0766
Smoking initiation among former smokers (years)					
<16	229	1.07 (0.94–1.23)	<16	102	1.10 (0.89–1.36)
16–26	1,805	1.04 (0.99–1.10)	16–26	1,024	1.12 (1.01–1.23)
≥26	282	0.99 (0.88–1.12)	≥26	189	1.10 (0.93–1.29)
p trend[4]		0.2259	p trend[4]		0.0757
Smoking initiation among current smokers (years)					
<16	185	0.96 (0.82–1.11)	<16	115	1.10 (0.90–1.36)
[16–26[	1,391	1.10 (1.03–1.17)	[16–26[	918	1.22 (1.10–1.36)
≥26	290	0.96 (0.85–1.08)	≥26	170	0.95 (0.80–1.13)
p trend[4]		0.4240	p trend		0.1266
Smoking initiation in relation with age at full-term pregnancy among former smokers[5] (years)					
Before	1,668	1.05 (0.99–1.11)	Before	947	1.11 (1.00–1.24)
After	257	1.01 (0.89–1.15)	After	171	1.10 (0.93–1.31)
$p_{heterogeneity}$		0.6179			0.9194

Table 3. Adjusted HRs of breast cancer in relation to cigarette smoking among all women (n = 322,988) and among women with data on passive smoking (n = 183,608), EPIC cohort 1992–2000 (Continued)

All women (n = 322,988)			Women with data on passive smoking (n = 183,608)		
	Cases	HR[1] (95% CI)		Cases	HR[1] (95% CI)
Smoking initiation in relation with age at full-term pregnancy among current smokers[5] (years)					
Before	1,257	1.10 (1.03–1.18)	Before	828	1.21 (1.08–1.36)
After	309	1.01 (0.90–1.13)	After	195	1.05 (0.88–1.24)
$p_{heterogeneity}$		0.0256			0.1471
Smoking initiation in relation with age at full-term pregnancy among ever smokers[5] (years)					
Before	2,925	1.06 (1.01–1.12)	Before	1,775	1.15 (1.04–1.27)
After	566	1.01 (0.92–1.10)	After	366	1.07 (0.93–1.22)
$p_{heterogeneity}$		0.31			0.38

[1]Adjusted for : BMI at recruitment (<18.5/18.5–25/25–30/≥30 kg/m^2), educational level (none or primary/professional/secondary/university/missing), ever use of oral contraceptives (yes/non/missing),ever use of menopausal hormone therapy (yes/no/missing), menopausal status at baseline (premenopausal/postmenopausal/unknown), parity and age at first full-term pregnancy (nulliparous/parous and age at FFTP ≥ 25 years/parous and age at FFTP < 25 years/missing), age at menarche (<12/12/13/≥14 years), alcohol consumption (0/0–10/>10 g ethanol), physical activity (inactive, moderately inactive, moderately active, active, missing).
[2]Women not exposed to passive smoke in their childhood (for centers that collected this information) nor living with a smoker nor being exposed at work at recruitment into the cohort.
[3]Women exposed to passive smoke either during their childhood (for centers that collected this information) or living with a smoker, or exposed at work at recruitment into the cohort, or all of these.
[4]Test for trend performed on the categorical variables without missing data and never smokers.
[5]Only for parous women.

(such as BMI, alcohol consumption or postmenopausal hormone therapy use) may have resulted in some residual confounding.

In the EPIC study, we observed that women exposed to passive smoking had an increased risk of breast cancer of similar magnitude compared to active smokers and that excluding passive smokers from the reference group led to higher risk estimates for active smokers. Most of the 150 epidemiological studies that have reported data regarding smoking and breast cancer over the past few decades have included passive smokers in their unexposed reference groups.[25] These studies have variably shown positive, inverse or null association, leading several authors to emphasize the need for a comprehensive measure of both active and passive smoking.[3,4,9,19] Indeed, removal of passive smokers from the reference category revealed risks associated with active smoking of a higher magnitude, suggesting that including passive smokers in the reference group may have biased previous findings toward the null.[4,18] In previous cohort studies, the associations observed with passive smoking were dependent on the quality of the passive exposure measures. When only residential exposure was available, little effect of passive smoking was shown.[19,26] When both lifetime occupational and residential exposures[23] or more quantitative measures of passive smoking exposures[8] were evaluated, an increased risk was observed. The results published on data from the Nurses' Health Study, however, did not show any increased risk with passive smoking exposure either at work or at home, but their evaluation of passive smoking exposure remained incomplete.[7,27] In a recent meta-analysis by Pirie *et al.*, no association between passive smoking and breast cancer risk was observed in prospective cohorts; however, no consideration was given in this analysis to the quality of passive exposure measures.[19]

Our finding that breast cancer risk is particularly high in women who started smoking before their FFTP is in agreement with previous results from cohort studies, which demonstrated an increase in risk in women who began smoking early in life.[5–11,17,26,28,29] This later result, though, might be confounded by smoking duration as women who started smoking early also tend to smoke for a longer duration. In addition, residual confounding by age at first birth is also possible as women with a later first birth, and therefore a higher breast cancer risk, have more chance to have started smoking before FFTP. However, when we looked at pack-years smoked at different periods of life, taking into account other periods of smoking, smoking before first birth was most strongly associated with an increased risk of breast cancer. There was also a decrease in risk of breast cancer after menopause. This last observation is in line with the recently published results of the Nurse's Health Study[7] and with one previous case–control study.[12] The relationship between smoking and breast cancer was also analyzed according to the hormone receptor status or the histological subtype of the tumor, with conflicting results.[8,30–32] In this analysis, we found a slightly higher risk for ER+PR+ than for ER−PR− tumors among current active smokers. This is in line with the results published recently by Luo *et al.*[8] and could imply that an estrogenic environment is necessary to allow carcinogenesis in cells that have been mutated by tobacco carcinogens.[13] In addition, in the EPIC study, the association between smoking (active or passive) and breast

Table 4. Adjusted HRs of breast cancer in relation to pack-years of smoking relevant to menarche, age at first birth and menopause, among all women with data on lifetime exposure (n = 243,730) and among women with data on lifetime exposure and passive smoking (n = 109,004), EPIC cohort 1992–2000

	All women[1] (n = 243,730)		Women with data on passive smoking[1] (n = 109,004)	
	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]
Passive exposure only			1,232	1.18 (1.04–1.35)
Smoking from menarche to before menopause, pack-years				
0	3,356	Reference	403	Reference
1–5	625	1.00 (0.83–1.21)	244	1.23 (0.91–1.67)
5–10	482	1.02 (0.82–1.27)	192	1.20 (0.83–1.72)
10–15	440	1.05 (0.82–1.34)	203	1.27 (0.85–1.90)
15–20	364	1.04 (0.80–1.35)	179	1.32 (0.86–2.01)
≥20	563	0.99 (0.74–1.32)	294	1.36 (0.87–2.13)
p for trend		0.5289		0.2544
Every increase of 20 pack-years		1.09 (0.93–1.27)		1.16 (0.92–1.46)
Smoking from menarche to before first birth, pack-years[3]				
0	3,222	Reference	560	Reference
1–5	1,392	1.00 (0.89–1.13)	728	0.98 (0.84–1.16)
5–10	443	1.23 (1.05–1.44)	198	1.31 (1.05–1.64)
10–15	117	1.33 (1.04–1.70)	32	1.06 (0.69–1.55)
15–20	33	1.42 (0.96–2.11)	11	1.59 (0.84–3.03)
≥20	13	1.33 (0.74–2.41)	3	0.88 (0.27–2.84)
p for trend		0.0035		0.0745
Every increase of 20 pack-years		1.73 (1.29–2.32)		1.71 (1.12–2.59)
Smoking after first birth to before menopause, pack-years[3]				
0	3,092	Reference	454	Reference
1–5	526	0.93 (0.79–1.08)	194	0.84 (0.65–1.08)
5–10	425	0.91 (0.75–1.12)	201	0.95 (0.68–1.33)
10–15	357	1.00 (0.78–1.29)	170	0.87 (0.58–1.31)
15–20	260	1.23 (0.91–1.68)	149	1.23 (0.77–1.97)
≥20	263	1.23 (0.88–1.74)	152	1.15 (0.68–1.92)
p for trend		0.0784		0.0694
Every increase of 20 pack-years		1.19 (0.96–1.47)		1.12 (0.81–1.55)
Smoking after menopause, pack-years				
0	2,387	Reference	367	Reference
1–5	445	0.96 (0.83–1.10)	234	1.02 (0.81–1.28)
5–10	181	0.79 (0.65–0.96)	98	0.80 (0.60–1.07)
10–15	61	0.72 (0.55–0.96)	32	0.72 (0.48–1.08)
15–20	24	0.77 (0.50–1.17)	11	0.74 (0.39–1.38)
≥20	12	0.64 (0.36–1.15)	4	0.46 (0.17–1.26)
p for trend		0.0087		0.0091
Every increase of 20 pack-years		0.63 (0.47–0.84)		0.53 (0.34–0.82)
Smoking after menopause without MHT, pack-years				
0	2,532	Reference	461	Reference
1–5	389	1.00 (0.87–1.15)	197	1.18 (0.96–1.46)
5–10	108	0.76 (0.60–0.95)	46	0.81 (0.57–1.15)

Table 4. Adjusted HRs of breast cancer in relation to pack-years of smoking relevant to menarche, age at first birth and menopause, among all women with data on lifetime exposure (n = 243,730) and among women with data on lifetime exposure and passive smoking (n = 109,004), EPIC cohort 1992–2000 (Continued)

	All women[1] (n = 243,730)		Women with data on passive smoking[1] (n = 109,004)	
	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]
≥10	60	0.78 (0.58–1.03)	20	0.75 (0.46–1.22)
p for trend		0.0141		0.0049
Every increase of 20 pack-years		0.67 (0.47–0.95)		0.65 (0.36–1.16)
Smoking after menopause with MHT, pack-years				
0	1,075	Reference	209	Reference
1–5	205	1.02 (0.81–1.29)	123	0.88 (0.64–1.21)
5–10	65	0.86 (0.63–1.18)	42	0.71 (0.47–1.07)
≥10	26	0.73 (0.47–1.13)	19	0.69 (0.40–1.18)
p for trend		0.2771		0.4668
Every increase of 20 pack-years		0.65 (0.37–1.12)		0.54 (0.26–1.12)

[1]In centers with available information on lifetime cigarette per day (*i.e.*, excluding France and Sweden).
[2]Adjusted for: BMI at recruitment (<18.5/18.5–25/25–30/≥30 kg/m^2), educational level (none or primary/professional/secondary/university/missing), ever use of oral contraceptives (yes/non/missing), ever use of menopausal hormone therapy (yes/no/missing), menopausal status at baseline (premenopausal/postmenopausal/unknown), parity and age at first full-term pregnancy (nulliparous/parous and age at FFTP ≥ 25 years/parous and age at FFTP < 25 years/missing), age at menarche (<12/12/13/≥14 years), alcohol consumption (0/0–10/>10 g ethanol), physical activity (inactive, moderately inactive, moderately active, active, missing); in the assessment of smoking during a specific period, smoking during the other life periods was adjusted for.
[3]Only among parous women.

cancer seemed to be limited to nonalcohol consumers. This is in contradiction with a previous report from the Collaborative Group on Hormonal Factor in Breast Cancer that reanalyzed 53 epidemiological studies and showed that smoking was not associated with breast cancer risk in women drinking no alcohol.[2] In contrast, in two cohort studies from Scandinavia and California, several of the measures of smoking exposure were strongly associated with an increased risk among nondrinkers.[9,26] As we did, these studies also excluded passive smokers from the reference group. This was not done in the previous report from the Collaborative Group. In addition, previous cohort studies (including all studies from the report of the Collaborative Group) had very short follow-up time, which may at least partially explain them missing the association. Besides, similarly to what has been previously reported,[22] our data did indicate a possible effect modification by BMI of the association between smoking and breast cancer with stronger associations among normal weight women. The stronger association observed among premenopausal women might actually be due to residual confounding by BMI as obese premenopausal women having a known lower risk of breast cancer are also less likely to smoke (smokers being generally leaner).

Tobacco smoke might affect breast cancer risk through direct or indirect effects of carcinogens contained in the smoke. Breast tissue has been shown, *in vitro* and *in vivo*, to undergo neoplastic transformation when exposed to certain carcinogens from tobacco smoke such as polycyclic hydrocarbons (PAH), aromatic amines and *N*-nitrosamines.[3,33] These carcinogens can form specific DNA adducts in breast tissue where they can cause DNA damages.[34] Endocrine disruptors contained in tobacco smoke such as PAH can also interfere with estrogen metabolism and induce the formation of genotoxic estrogen metabolites.[35] The later effect might depend on breast differentiation: the carcinogenic effect of estrogen metabolites might be more important in the less differentiated breast.[12,36] The higher breast cancer risk observed in women who started smoking before their FFTP, and therefore before full breast differentiation, is in agreement with such hypothesis. An antiestrogenic effect able to protect against breast cancer has also been hypothesized, through changes in hepatic estrogen metabolism[37,38] or by inhibiting the aromatization of androgens into estrogens,[37–40] although a large pooled analysis with data from 13 studies, including EPIC, showed that BMI-adjusted mean serum concentrations of estradiol and other sex hormones were higher in heavy smokers than in nonsmokers.[41] Such a protective effect, unless it is of outstanding magnitude, is expected to be most apparent when circulating levels of estrogens are low, that is after menopause, among MHT non users, as observed in previous studies.[12,13] Our observation of a decrease in breast cancer risk with pack-years smoked after menopause, particularly among women nonusers of MHT, is compatible with the hypothesis of a moderate antiestrogenic effect of tobacco.

The risk associated with smoking exposure may also vary according to genetic susceptibility, as found in a number of studies (reviewed by Terry and Goodman[42], which indeed might explain part of the differences observed across EPIC

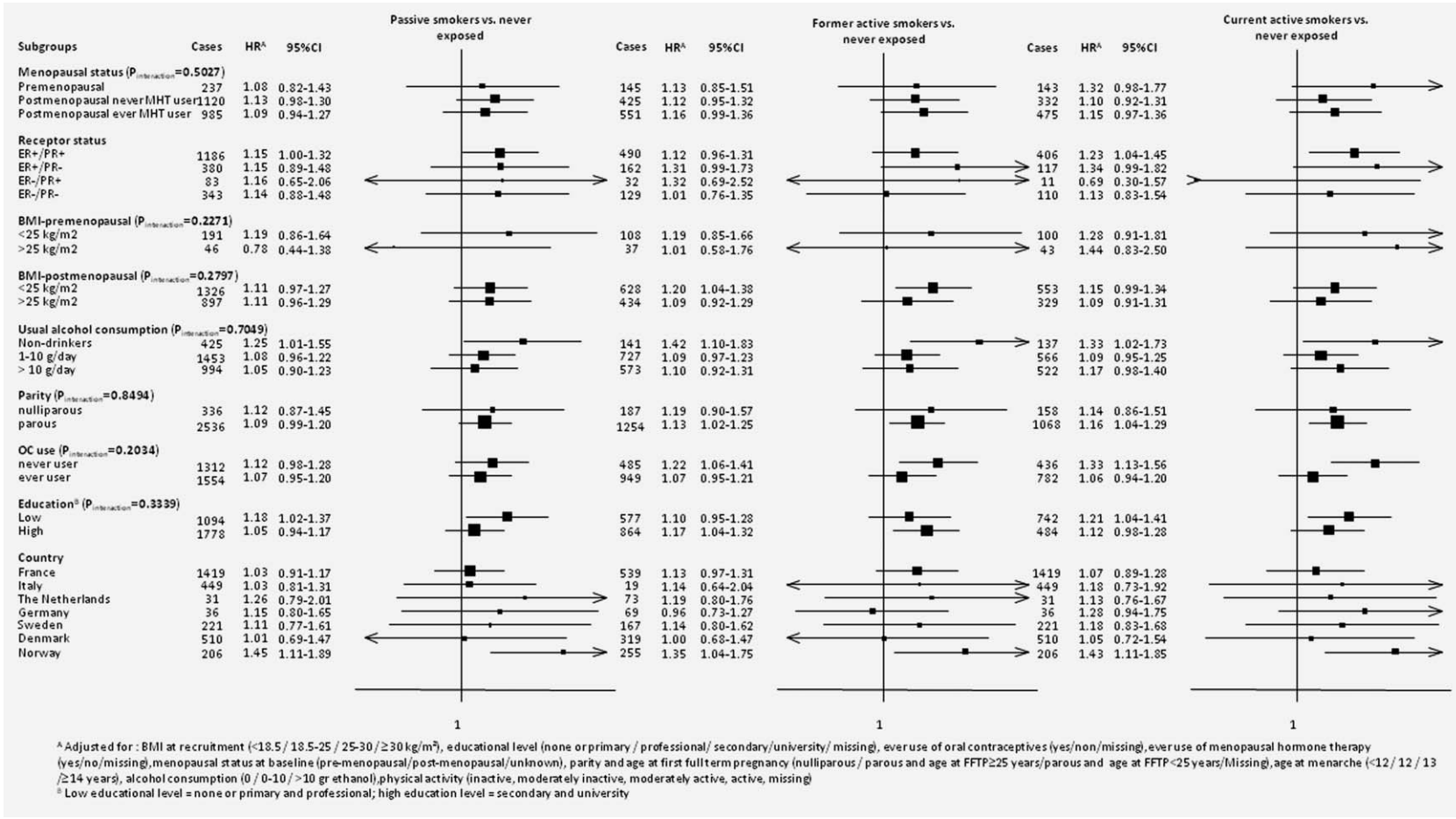

Figure 1. Adjusted HRs of breast cancer in relation to cigarette smoking according to menopausal status, hormone receptor status of the tumor and other subgroups of breast cancer risk factors, among women with information on adult passive exposure (n = 183,608). EPIC cohort 1992–2000.

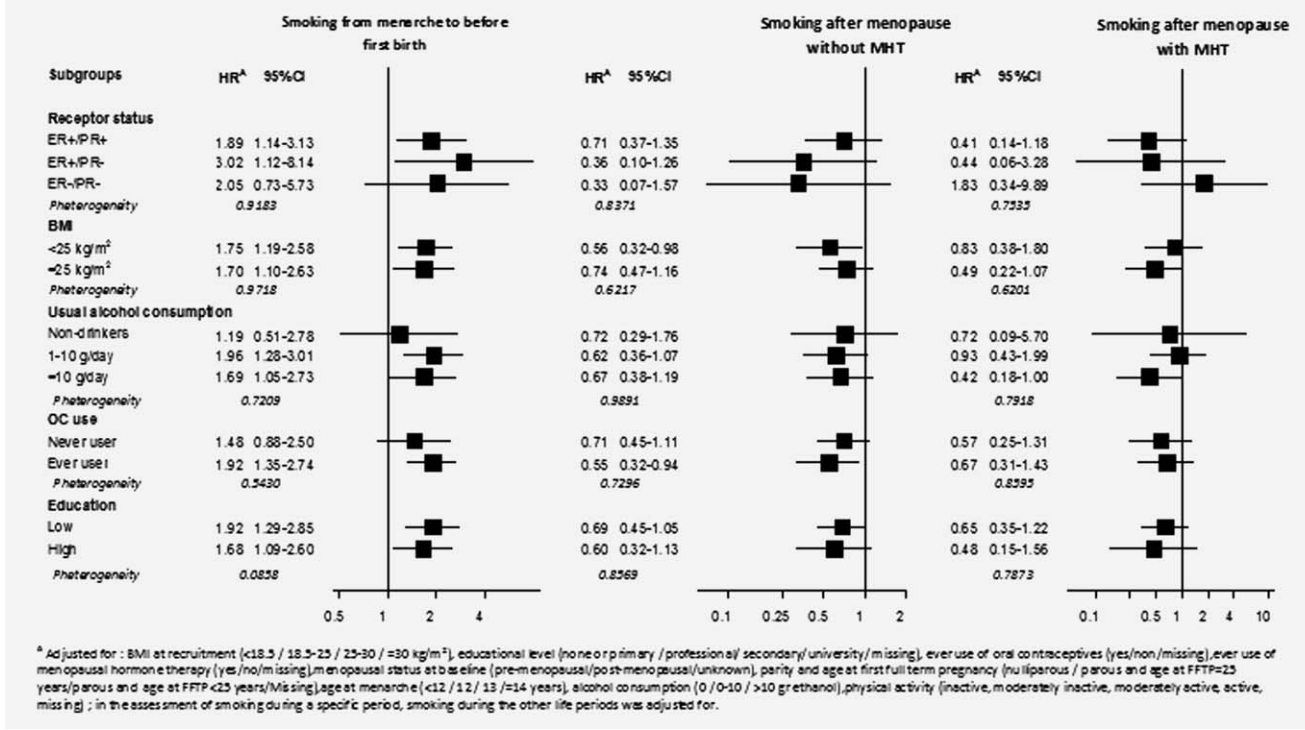

Figure 2. Adjusted HRs of breast cancer in relation to every increase of 20 pack-years of smoking relevant to menarche, age at first birth and menopause, according to hormone receptor status of the tumor and other subgroups of breast cancer risk factors, among all women with data on lifetime exposure (n = 243,730). EPIC cohort 1992–2000.

countries. The deleterious effect of smoking in women with a familial or genetic predisposition was found in high-risk breast cancer families[43] but not among carriers of BRCA mutations.[44] Some studies examined the risk according to genotypes that activate or detoxify tobacco compounds in the human body or in genes related to DNA repair, with no clear overall pattern of risk.[42] For example, smokers with the NAT2 (*N*-acetyltransferase 2, an enzyme that detoxifies aromatic amines contained in tobacco smoke) slow acetylator genetically determined phenotype might be at a higher risk of breast cancer than those with intermediate or high acetylation phenotype.[45,46] Biological mechanisms that could explain the similarity of the risk among passive and active smokers still have to be identified. Differences in the composition of mainstream and sidestream smoke have been observed[25] and the faster absorption in blood of vapor-phase components (predominant in sidestream smoke) than particulate-phase components supports a role of passive smoking on breast cancer.[47] A "low dose effect" of passive smoking has been hypothesized, with the assumption that the effect modification by the NAT2 genotype might be amplified at low doses.[48,49] Studies have failed, however, to confirm this hypothesis[18,46] and in the Breast and Prostate Cohort consortium (BPC3), a consortium of six large prospective cohort studies including EPIC, the risk of breast cancer associated with smoking was not modified by NAT2 genotypes.[50]

In conclusion, our results are consistent with an increase in breast cancer risk in women exposed to smoking, passively or actively, when compared to women never exposed to tobacco smoke during adult life. They are supportive of a carcinogenic effect of tobacco most potent on mammary cells before pregnancy and therefore highlight the need of early age prevention programs. Our findings also emphasize the fact that passive smoking might be as important as active smoking in terms of breast cancer risk and stress the need to distinguish passive smokers from never smokers when analyzing the relationship between smoking and breast cancer.

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