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The fraction of breast cancer attributable to smoking: The Norwegian women and cancer study 1991–2012

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Background: Results from several recent cohort studies on smoking and breast cancer incidence and mortality suggest that the burden of smoking on society is underestimated. We estimated the fraction of breast cancer attributable to smoking in the Norwegian Women and Cancer Study, a nationally representative prospective cohort study.

Methods: We followed 130 053 women, aged 34–70 years, who completed a baseline questionnaire between 1991 and 2007, through linkages to national registries through December 2012. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), while adjusting for confounders. Never smokers, excluding passive smokers, were used as the reference group in all main analyses. We estimated attributable fractions (AFs) % in smokers and in the population (PAFs) % with 95% CIs.

Results: Altogether, 4132 women developed invasive breast cancer, confirmed by histology. Compared with never active, never passive smokers, ever (former and current) smokers had an overall risk of breast cancer that was 21% higher (HR = 1.21; 95% CI = 1.08–1.34). For ever smokers, the AF was 17.3% (95% CI = 7.4–25.4) and for the population the PAF of breast cancer was 11.9% (95% CI = 5.3–18.1). For passive smokers, the PAF of breast cancer was 3.2% (95% CI = 1.0–5.4). When we applied PAF estimates for ever smoking on the 2907 new breast cancer cases among Norwegian women aged 35+ at diagnosis in 2012, this yielded 345 (95% CI = 154–526) breast cancer cases that could have been avoided in the absence of active smoking that year.

Conclusions: In smokers, one in six and in the population, one in nine breast cancer cases could have been avoided in the absence of active smoking. Our findings support the notion that the global cancer burden due to smoking is substantially underestimated.

Today, there is an international consensus that there is sufficient evidence to identify mechanisms by which passive and active cigarette smoking may cause breast cancer (California Environmental Protection Agency, 2005; Collishaw *et al*, 2009; Johnson *et al*, 2011; International Agency for Research on Cancer, 2012; US Department of Health and Human Services, 2014), but a disagreement whether the evidence is sufficient (California Environmental Protection Agency, 2005; Collishaw *et al*, 2009; Johnson *et al*, 2011) or not (International Agency for Research on Cancer, 2012; US Department of Health and Human Services, 2014) to infer a causal relationship.

However, results from several recent cohort studies, not included in the above-listed expert reports, on smoking and breast cancer incidence (Bjerkaas *et al*, 2013; Gaudet *et al*, 2013; Rosenberg *et al*, 2013; Dossus *et al*, 2014; Nyante *et al*, 2014; Catsburg *et al*, 2015; Gram *et al*, 2015) and mortality (Bjerkaas *et al*, 2014; Carter *et al*, 2015) suggest that the burden of smoking on society is underestimated.

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This was suggested by (Carter *et al*, 2015) based on the results from pooled data from five contemporary US cohorts. They show a substantial portion of excess mortality among current smokers due to associations with diseases, one being breast cancer, that have not been formally established as caused by smoking (Carter *et al*, 2015).

Findings from the seven above-listed large cohort studies (Bjerkaas *et al*, 2013; Gaudet *et al*, 2013; Rosenberg *et al*, 2013; Dossus *et al*, 2014; Nyante *et al*, 2014; Catsburg *et al*, 2015; Gram *et al*, 2015), all show a relationship between smoking and breast cancer that is consistent with causality. Four (Bjerkaas *et al*, 2013; Gaudet *et al*, 2013; Rosenberg *et al*, 2013; Dossus *et al*, 2014) were included in a review from 2014 (Glantz and Johnson, 2014) and in addition two (Nyante *et al*, 2014; Catsburg *et al*, 2015) more of these studies in a meta-analysis from 2015 (Macacu *et al*, 2015). Both reports (Glantz and Johnson, 2014; Macacu *et al*, 2015) conclude that both active and passive smoking are associated with a modest, but real increase in the risk of breast cancer.

Alcohol consumption is an established causal factor for breast cancer. When the causality between smoking and breast cancer is discussed, the issue of confounding by alcohol consumption is usually raised. This has for many years been the main argument for not having breast cancer established as a smoking-related cancer. In contradiction to this belief, we found that the smoking-related risk of breast cancer was neither confounded by alcohol in the study from the European Prospective Investigation into Cancer and Nutrition (EPIC) (Dossus *et al*, 2014), nor in the unique Multi Ethnic Cohort (Gram *et al*, 2015).

The International Agency for Research on Cancer estimated that globally, breast cancer incidences have increased sharply by more than 20% from 2008 to 2012, when 1.7 million women were diagnosed with breast cancer (Ferlay *et al*, 2013). In Norway, there has been an increase in incidence for both lung and breast cancer during the last 50 years. In 2012, close to 3000 new breast cancer cases were diagnosed, of which $\sim$20% were in women under the age of 50 years (Cancer Registry of Norway, 2014).

Among Norwegian women, the prevalence for daily smoking was 23% in 1954, the peak was at 37% in 1970 and then, the prevalence of daily smokers stabilised at around 32% for the rest of the century (Kjønstad *et al*, 2000). A similar trend has been seen in Oceanic, European and North American countries, where the prevalence of smoking among women has significantly decreased over the past three decades (Eriksen *et al*, 2015). In 2015, altogether 21% of Norwegian women aged 16–74 years were current (daily or occasional) smokers (Statistics Norway, 2016).

Worldwide, more women than in the previous generations initiate smoking in their teens (Giovino *et al*, 2012; Eriksen *et al*, 2015). In the study by Bjerkaas *et al* (2013), comprising more than 300 000 Norwegian women, we found that the mean age at smoking initiation decreased, and the proportion of women who started to smoke before their first childbirth increased steadily from 62% for those born before 1946 to 94% for those born after 1955.

The majority of Norwegian middle-aged women are ever (i.e., either former or current) smokers who started as teenagers (Gram *et al*, 2005; Helleve *et al*, 2010; Bjerkaas *et al*, 2013). We utilised the Norwegian Women and Cancer Study, a nationally representative prospective cohort, to estimate the fraction of breast cancer attributable to passive and ever smoking and the number of breast cancer cases that could have been avoided in the absence of smoking in Norway in 2012.

MATERIALS AND METHODS

Study population. The Norwegian Women and Cancer Study cohort profile has been previously described in detail (Lund *et al*, 2003; Lund *et al*, 2008). Briefly, the Central Population Register selected a random sample of women according to year of birth. Subsequently, an invitation to participate in the study, with a baseline questionnaire and a pre-stamped return envelope enclosed was mailed to each woman. The National Data Inspectorate and the Regional Committee for Medical Research Ethics approved the study. All women gave an informed consent https://site.uit.no/nowac/.

Women who completed a questionnaire during three waves of data collection: 1991–1992, 1996–1997 and 2003–2007 (172 478) were included. The overall response rate was 52.7%. We excluded women with prevalent cancer (7091), who had emigrated (116), died before start of follow-up (56), who were born after 1957 (3166), who had with missing information on ever (1312) and passive (5271) smoking status, or on important covariates (education, height, current weight, menopausal status, parity, age at first birth and alcohol consumption; 25 413). Altogether, 1248 women with breast cancer were excluded in this process. The cohort comprised the 130 053 remaining women.

Data collection. At enrolment, the women reported whether they had ever smoked, the average number of cigarettes smoked per day at different ages, if they currently smoked daily, and if their parents smoked during their childhood. Based on the answer to these questions, we computed age at smoking initiation, and the number of years smoking. We also calculated pack-years of smoking as the number of cigarettes smoked per day, divided by 20, and multiplied by the duration of smoking in years. For parous smokers, we calculated years of smoking before first childbirth as the age in years at the birth of the first child minus the age at smoking initiation.

Outcome assessment. We followed the women through linkages to the Cancer Registry of Norway and the Norwegian Central Population Register, to identify all cancer cases, emigrations and deaths, respectively, using the unique national 11-digit personal identification number. We calculated person-years from the start of follow-up to the date of any incident cancer diagnosis (except basal cell carcinoma), emigration, death or the end of follow-up 31 December 2012, whichever came first. We classified breast cancer cases according to the original codes in the International Classification of Diseases, Seventh Revision including estrogen and progesterone hormone tumour receptor status.

Statistical analysis. For the distribution of selected characteristics of the study population, we calculated percentages (%) or means with standard deviations ($\pm$ s.d.). We estimated crude breast cancer incidence rates by dividing the number of cases by the total number of person-years in that exposure (never, passive, former, current) category (Breslow and Day, 1987). The rates were then age-adjusted to the world standard population (http://seer.cancer.gov/stdpopulations/).

We stratified all models by birth cohort and cohort enrolment to control for calendar and age cohort effects, questionnaire design and duration of follow-up. We used the Cox proportional hazards model with age as the underlying time scale, to estimate crude and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between breast cancer and different measures of smoking exposure. Smoking exposure was defined using smoking status at cohort entry (never, passive, former, current or ever); for women who had ever smoked, further exposures were defined using age at smoking initiation ($<$15, 15–19, 20–24, $\geqslant$25 years), smoking duration ($\leqslant$10, 11–20, 21–30, $>$30 years); and number of pack-years of smoking ($\leqslant$5, 6–10, 11–15, $>$15). The reference group is never active, never passive smokers throughout the manuscript, unless otherwise noted. We determined the associations between different measures of smoking and breast cancer for the entire study population and by menopausal and parous status.

We included covariates, that changed the HR estimate by 5%, when applicable, that could potentially confound the association between smoking and breast cancer. We included the following variables in the final multivariate models; age at enrolment, years of education (<10, 10–12, 13–16, $\geqslant 17$), age at menarche (<13, 13–14, $\geqslant 15$), ever oral contraceptives use (yes, no), a variable including nulliparous and a combination of total number of births (1, 2, $\geqslant 3$) and of age at first childbirth (age <20, 20–24, 25–29, $\geqslant 30$) for a total of 13 categories, family history of breast cancer in the mother (yes, no), body mass index (calculated from current height and weight (<20, 20–24.9, 25–29.9, $\geqslant 30\,\mathrm{kg\,m^{-2}}$)], menopausal status (yes, no), postmenopausal hormone therapy use (never, former, current) and average alcohol consumption, based on the content of pure alcohol in different sorts of beverages and portion sizes, as grams of alcohol per day (0, 0.1–1.40, 4.1–10, >10)). Women who reported to be teetotalers and those answering 'seldom or never' had their alcohol consumption set to 0. We did sensitivity analyses for women who were asked about and had reported on ever attending mammographic screening (yes, no), 52.5% (76 483).

For parous women, we estimated breast cancer risk by category of age at smoking initiation in relation to first childbirth (after, around or within 5 years before first childbirth, or $\geqslant 5$ years before), compared with parous never smokers overall, restricted to non-drinkers of alcohol and stratified for age (<50; $50+$), and tumour hormone receptor status ((estrogen positive and negative), and (progesterone positive and negative)) at diagnosis. We estimated breast cancer risk overall according to smoking initiation in relation to first birth stratified by number of years smoked ($\leqslant 10$, 11–20, >20).

We tested for linear trends across categories of smoking exposures variables, excluding never smokers, by assigning the median a score in order to account for the distance between categories, treating the variable as continuous in the analyses. We tested for heterogeneity in the association of breast cancer with smoking status (ever, never) by postmenopausal or parous (yes, no) status, alcohol abstinence (yes, no), age at diagnosis <50 (yes, no) and ever attending mammographic screening (yes, no), using the Wald test.

We calculated the attributable fraction (AF) (%) among passive and ever smokers and the corresponding population attributable fraction (PAF) (%) to indicate what proportion of the breast cancer cases that could have been prevented in smokers and in the population in the absence of smoking. We used the formula $\mathrm{PAF} = \frac{\mathrm{Pe}\times(\mathrm{RRe}-1)}{\mathrm{Pe}\times\mathrm{RRe}+(1-\mathrm{Pe})}$ where the notation Pe = the proportion of persons in the population exposed to the risk factor (i.e., passive and ever smokers) and $\mathrm{RR_e}$ = the relative risk in the exposed compared with the unexposed group (i.e., passive and ever compared with never smokers) (World Health Organization, 2012). Likewise, we estimated the AF (%) and PAF (%) by age at diagnosis <50 years (yes, no). We calculated the two-sided 95% CIs for the AFs and PAFs using the PUNAF Stata module (Newson, 2010).

We calculated the number of breast cancer cases attributable to smoking in women aged 35 years and older using two approaches. First, we applied the estimated PAF values with the 95% CIs for passive and ever smoking to the observed number of new breast cancer cases. Next, we applied the never-smoker age-adjusted incidence rate of breast cancer in the cohort to the population in Norway in 2012 and calculated the number of breast cancer cases expected in the absence of smoking. Then we calculated the number of breast cancer cases attributable to smoking by subtracting the expected cases from the number observed (Peto *et al*, 1992; Cancer Registry of Norway, 2014). Finally, we estimated the overall multivariate-adjusted HR with 95% CIs for ever smokers, compared with a reference group including both never and passive smokers. We estimated the corresponding PAF (%) with 95% CIs.

We performed the analyses using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA) or in STATA version 12.0 (Stata Corp, College Statistics, TX, USA) and considered two-sided *P*-values <0.05 as statistically significant.

RESULTS

At enrolment, the mean age of the participants was 48.9 (± 8.2 s.d.) years. Of these women, 67.5% ($n = 87\,844$) reported to be ever (current 31.9%, former 35.6%) smokers, with mean initiation at age 18.7 (± 4.9 s.d.) and 10.2 (± 8.9 s.d.) pack-years of smoking. Among parous women, 62.2% ($n = 73\,356$) reported smoking with a mean duration of 4.9 (± 6.5 s.d.) years before their first childbirth. During the more than 1.7 million person-years of observation (mean follow-up time was 13.4 (± 6.3 s.d.) years, we ascertained 4132 incident cases of primary invasive breast cancer, confirmed by histology. Altogether 90.6% ($n = 117\,869$) of the women reported to be alcohol drinkers with a mean alcohol consumption of 3.5 (± 5.1 s.d.) grams per day. The age-standardised incidence rate for breast cancer among never, passive and ever smokers was 185.5, 227.5 and 235.3 per 100 000 person-years, respectively.

Table 1 shows that ever compared with passive and never smokers were younger at breast cancer diagnosis, at first childbirth and at menopause; they were less likely to have higher education, more likely to have used hormonal contraceptives and postmenopausal hormone therapy and to consume alcohol. The alcohol drinkers were consuming more alcohol (Table 1).

Table 2 shows that compared with never smokers, both the unadjusted and multivariate adjusted HRs for breast cancer was increased significantly for passive, former and current smokers. Compared with the reference group, passive had an overall 18% higher (HR = 1.18; 95% CI = 1.05–1.33) and ever (former and current) smokers a 21% higher (HR = 1.21; 95% CI = 1.08–1.34) risk of breast cancer. We found similar HR estimates when we stratified by menopausal and parous status at entry (Table 2).

The association between ever/never smoking and risk of breast cancer was neither significantly different for postmenopausal (yes, no; Wald χ^2, $P_{\mathrm{heterogeneity}} = 0.55$) nor parous (yes, no; Wald χ^2, $P_{\mathrm{heterogeneity}} = 0.42$) status, nor for mammographic screening attendance (yes, no; Wald χ^2, $P_{\mathrm{heterogeneity}} = 0.18$). Compared with a reference group which also included passive smokers, ever smokers no longer had a statistically significant increased risk for breast cancer, but achieved one of borderline statistical significance (HR = 1.08; 95% CI = 1.00–1.15).

Compared with parous never smokers, ever smokers who had smoked for 5 or more years before giving birth had a 29% higher (HR = 1.29; 95% CI = 1.14–1.46) risk of breast cancer, after adjustment. For parous ever smokers, significant associations with breast cancer risk were observed for smoking initiation in relation to first birth for women overall, for women who did not drink alcohol, and for women diagnosed before age 50 years (Table 3). When we used each of the four tumour hormone receptor status ((estrogen positive and negative), and (progesterone positive and negative)) tumours at diagnosis as an outcome, we found similar associations with breast cancer risk for smoking initiation in relation to first birth (data not shown). The association between ever/never smoking and risk of breast cancer was neither significantly different for non-drinkers (yes, no; Wald χ^2, $P_{\mathrm{heterogeneity}} = 0.94$) nor for age at diagnosis <50 years (yes, no; Wald χ^2, $P_{\mathrm{heterogeneity}} = 0.44$).

Figure 1 shows that, after adjustment and stratification by years of smoking ($\leqslant 10$, 11–20, >20), within all three groups, women who had smoked for 5 or more of these years before the first childbirth had a more than 20% (HR = 1.23; 95% CI = 1.07–1.40,

Table 1. Selected characteristics of women by smoking status at enrolment, Norwegian Women and Cancer Study, 1991–2012 (*N* = 130 053)

	Never smokers		Passive smokers		Ever (former and current) smokers	
Characteristics	***N* (%)**	**Mean (± s.d.)**	***N* (%)**	**Mean (± s.d.)**	***N* (%)**	**Mean (± s.d.)**
Women	14 867 (11.4)		27 342 (21.0)		87 844 (67.5)	
Age at enrolment		50.7 (8.7)		49.0 (8.2)		48.5 (8.0)
Person-years	200 397 (11.5)		379 082 (21.7)		1 168 105 (66.8)	
Follow-up years		13.5 (6.1)		13.9 (6.3)		13.3 (6.3)
Primary invasive breast cancers	411 (9.9)		908 (22.0)		2813 (68.1)	
Age at diagnosis		58.9 (7.6)		57.6 (7.6)		56.8 (7.3)
Diagnosis before age 50 years	55 (13.4)		154 (17.0)		522 (18.6)	
Premenopausal breast cancer	57 (13.9)		162 (17.8)		519 (18.5)	
Family history of breast cancer	818 (5.5)		1476 (5.4)		4568 (5.2)	
Higher education ⩾13 years	7909 (53.2)		13 835 (50.6)		34 347 (39.1)	
Age at menarche		13.3 (1.4)		13.3 (1.4)		13.3 (1.4)
Age at menopause		49.4 (4.5)		49.1 (4.7)		48.2 (4.9)
Ever hormonal contraceptive use	6452 (43.4)		14 464 (52.9)		54 815 (62.4)	
Parous women	13 157 (88.5)		24 799 (90.7)		80 026 (91.1)	
Number of children		2.4 (1.4)		2.3 (1.2)		2.1 (1.1)
Age at first childbirth		25.1 (4.3)		24.6 (4.3)		23.6 (4.4)
Postmenopausal	6185 (41.6)		2788 (35.8)		32 151 (36.6)	
Ever postmenopausal hormone use	3196 (21.5)		5824 (21.3)		21 961 (25.0)	
Non-drinkers	3910 (26.3)		3855 (14.1)		4480 (5.1)	
Alcohol consumption (g per day)[a]		2.0 (3.5)		2.8 (4.0)		4.0 (5.6)
BMI ($kg\,m^{-2}$)[b]		24.3 (3.9)		24.4 (4.0)		24.1 (3.9)
Physical activity score[c]		5.8 (1.8)		5.7 (1.8)		5.7 (1.9)

Abbreviation: s.d. = standard deviation.
[a]Among women who consumed alcohol, expressed in grams per day.
[b]Body mass index; weight in kilograms divided by the square of the heights in metres.
[c]Physical activity score in 10 categories.

HR = 1.48; 95% CI = 1.26–1.73, and HR = 1.32; 95% CI = 1.07–1.63) significantly higher risk of breast cancer compared with the corresponding reference group.

In ever smokers, the AF of breast cancer was 17.3% (95% CI = 7.4–25.4) overall and 25.6% (95% CI = 0.76–44.3) for those diagnosed before age 50 years. Figure 2 shows that the PAF of breast cancer was 3.2% (95% CI = 1.0–5.4) for passive, and 11.9% (95% CI = 5.3–18.1) for ever smoking. For women <50 years at diagnosis, the PAF of breast cancer was 18.2% (95% CI = 0.9–32.5) for ever smoking. Our PAF estimates for ever smoking applied on the 2907 new breast cancer cases among Norwegian women aged 35+ at diagnosis in 2012, yielded 345 (95% CI = 154–526) breast cancer cases that could have been avoided in the absence of smoking. The difference between the expected ($n = 2\,623$) and observed ($n = 2907$) number of breast cancer cases derived from the never-smoker age-adjusted incidence rate of breast cancer was 284.

Compared with a reference group that also included passive smokers, ever smokers had an overall risk of breast cancer that was 8% higher (HR = 1.08; 95% CI = 1.00–1.15). The corresponding PAF of breast cancer was 4.9% (95% CI = 0.2–9.3) for ever smoking.

DISCUSSION

To our knowledge, the present study is the first to estimate the fraction of breast cancer attributable to passive and ever smoking based on a nationally representative prospective cohort study. We found that in smokers, one in six and in the population, one in nine breast cancer cases could have been avoided in the absence of active smoking. These numbers are of a magnitude that can explain some of the global increase in breast cancer incidence.

A recent publication discussing six factors contributing to achieving the 25 × 25 target of non-communicable disease mortality, does understandably not list breast cancer as one of the many disease outcomes that will be reduced with declining tobacco use (Kontis *et al*, 2014). Globally, in women aged 30–69 years, which is the target age for the 25 × 25 strategy, breast cancer is diagnosed in one out of every five female cancer diagnoses and is the most common form of cancer deaths worldwide (Ferlay *et al*, 2013).

As described (California Environmental Protection Agency, 2005; Collishaw *et al*, 2009; Johnson *et al*, 2011; International Agency for Research on Cancer, 2012; US Department of Health and Human Services, 2014), there is strong support for the biological plausibility of the association between smoking and breast cancer that we base our AF and PAF estimates on in the present study. The possibility that cigarette smoking acts at a relatively early stage in the carcinogenic process and thereby also increases the risk of ductal carcinoma *in situ* of the breast has been suggested (Kabat *et al*, 2010), but not confirmed. We use only invasive breast cancer cases, confirmed by histology, in the present study.

An important strength of our study is that it is representative of the Norwegian middle-aged female population, born between 1927 and 1957, both according to exposure and outcome. We know

Table 2. Crude-[a] and multivariate-[b] adjusted hazard ratio (HR) estimates for breast cancer with 95% confidence intervals (CIs) for different measures of smoking exposures overall and stratified by menopausal and parous status, Norwegian Women and Cancer Study, 1991–2012

	All women ($N=130\,053$)			Premenopausal ($n=69\,561$)		Postmenopausal ($n=127\,422$)		Parous ($n=117\,936$)		Nulliparous ($n=12\,117$)	
Smoking exposures	**Cases (*n*)**	**HR[a] (95% CI)**	**HR[b] (95% CI)**	**Cases (*n*)**	**HR[b] (95% CI)**	**Cases (*n*)**	**HR[b] (95% CI)**	**Cases (*n*)**	**HR[b] (95% CI)**	**Cases (*n*)**	**HR[b] (95% CI)**
Smoking exposures											
Never[c]	411	1 (ref)	1 (ref)	57	1 (ref)	354	1 (ref)	352	1 (ref)	59	1 (ref)
Passive	908	1.19 (1.06–1.33)	1.18 (1.05–1.33)	162	1.33 (0.98–1.81)	746	1.15 (1.01–1.38)	807	1.2 (1.06–1.36)	101	1.15 (0.83–1.59)
Former	1421	1.23 (1.10–1.37)	1.2 (1.07–1.34)	233	1.27 (0.95–1.71)	1188	1.18 (1.04–1.34)	1283	1.24 (1.10–1.40)	138	1.1 (0.81–1.51)
Current	1392	1.22 (1.10–1.36)	1.22 (1.09–1.37)	286	1.33 (0.99–1.79)	1106	1.19 (1.04–1.35)	1243	1.28 (1.13–1.44)	149	1.11 (0.81–1.52)
Ever	2813	1.22 (1.10–1.36)	1.21 (1.08–1.34)	519	1.3 (0.98–1.73)	2294	1.18 (1.05–1.33)	2526	1.26 (1.12–1.41)	287	1.11 (0.83–1.48)
Age at initiation (years)											
25+	177	1.08 (0.91–1.29)	1.08 (0.91–1.30)	14	0.64 (0.36–1.16)	163	1.13 (0.93–1.37)	155	1.11 (0.92–1.34)	22	1.03 (0.63–1.69)
20–24	786	1.26 (1.12–1.42)	1.22 (1.08–1.38)	127	1.36 (0.99–1.87)	659	1.21 (1.05–1.38)	692	1.25 (1.10–1.42)	94	1.22 (0.88–1.71)
15–19	1681	1.21 (1.09–1.35)	1.21 (1.08–1.36)	362	1.36 (1.02–1.83)	1 319	1.16 (1.02–1.32)	1 532	1.27 (1.13–1.44)	149	1.03 (0.75–1.41)
<15	169	1.34 (1.11–1.63)	1.31 (1.07–1.59)	16	0.95 (0.52–1.74)	153	1.35 (1.09–1.67)	147	1.38 (1.12–1.69)	22	1.25 (0.73–2.13)
P-trend[d]		0.29	0.27		0.026		0.85		0.13		0.8
Smoking duration											
0–10	562	1.19 (1.05–1.35)	1.18 (1.04–1.34)	119	1.3 (0.94–1.79)	443	1.16 (1.00–1.34)	518	1.23 (1.07–1.41)	44	0.97(0.66–1.44)
11–20	750	1.21 (1.07–1.37)	1.18 (1.04–1.33)	197	1.3 (0.96–1.76)	553	1.14 (0.99–1.32)	657	1.2 (1.05–1.37)	93	1.25 (0.89–1.75)
21–30	859	1.24 (1.10–1.39)	1.22 (1.08–1.38)	169	1.32 (0.96–1.80)	690	1.19 (1.04–1.37)	776	1.29 (1.13–1.47)	83	1.06 (0.75–1.50)
>30	642	1.25 (1.11–1.42)	1.26 (1.10–1.44)	34	1.25 (0.78–1.98)	608	1.24 (1.07–1.42)	575	1.33 (1.15–1.52)	67	1.09 (0.76–1.58)
P-trend[d]		0.35	0.25		0.87		0.32		0.14		0.87
Number of pack-years[e]											
0–5	1008	1.15 (1.03–1.30)	1.15 (1.02–1.29)	213	1.29 (0.96–1.75)	795	1.12 (0.98–1.28)	929	1.19 (1.06–1.35)	79	0.96 (0.68–1.36)
6–10	612	1.3 (1.14–1.49)	1.18 (1.04–1.34)	134	1.25 (0.91–1.72)	478	1.15 (0.98–1.28)	551	1.22 (1.07–1.40)	61	1.1 (0.77–1.59)
11–15	519	1.32 (1.16–1.49)	1.31 (1.14–1.49)	103	1.42 (1.01–1.99)	416	1.28 (1.10–1.49)	462	1.37 (1.19–1.58)	57	1.18 (0.81–1.71)
>15	674	1.19 (1.05–1.35)	1.29 (1.14–1.47)	69	1.28 (0.88–1.85)	605	1.27 (1.10–1.46)	584	1.35 (1.18–1.55)	90	1.24 (0.89–1.75)
P-trend[d]		0.004	0.007		0.79		0.012		0.008		0.09

[a]Adjusted for age.
[b]Adjusted for age, duration of education, hormone therapy, age at menarche, family history of breast cancer, age at first birth, number of children, hormonal contraceptive use, menopausal status, alcohol consumption and BMI, all at enrolment.
[c]Never-active, never-passive smokers as reference group.
[d]Test for trend excluding never smokers.
[e]Number of cigarettes smoked per day multiplied by number of years smoked, divided by 20.

Table 3. Crude-[a] and multivariate-[b] adjusted hazard ratio (HR) estimates with 95% confidence intervals (CIs) for breast cancer among parous women according to smoking initiation in relation to first birth for ever smokers, overall, restricted to non-drinkers and by age at diagnosis, Norwegian Women and Cancer Study, 1991–2012

	All parous women ($N=117\,930$)			Non-drinkers of alcohol		Age at diagnosis <50 years		Age at diagnosis 50+ years	
Smoking exposures	**Cases ($n=2877$)**	**HR[a] 95% CI**	**HR[b] 95% CI**	**Cases ($n=189$)**	**HR[b] 95% CI**	**Cases ($n=514$)**	**HR[b] 95% CI**	**Cases ($n=2363$)**	**HR[b] 95% CI**
Never[c]	352	1.00 (ref)	1.00 (ref)	84	1.00 (ref)	48	1.00 (ref)	304	1.00 (ref)
Ever, time of smoking initiation									
After first birth	372	1.08 (0.93–1.25)	1.1 (0.95–1.29)	17	0.81 (0.47–1.40)	48	0.97 (0.64–1.49)	324	1.13 (0.96–1.33)
Around or <5 years before first birth	948	1.16 (1.03–1.32)	1.17 (1.03–1.33)	44	1.16 (0.78–1.72)	184	1.25 (0.89–1.76)	764	1.16 (1.01–1.34)
⩾5 years before	1205	1.4 (1.24–1.58)	1.29 (1.14–1.46)	44	1.38 (0.95–2.02)	234	1.48 (1.10–1.44)	971	1.26 (1.11–1.45)
P-trend[d]		*<0.0001*	*0.01*		*0.009*		*0.01*		*0.1*

[a]Adjusted for age.
[b]Adjusted for age, duration of education, hormone therapy, age at menarche, family history of breast cancer, age at first birth, number of children, hormonal contraceptive use, menopausal status, alcohol consumption when applicable and BMI all at enrolment.
[c]Never, excluding active and passive, smokers as reference group.
[d]Test for trend excluding never smokers.

from our previous studies that the smoking exposure (Gram *et al*, 2009; Gram *et al*, 2013) and the breast cancer incidence (Lund *et al*, 2008) reflect known smoking patterns (Kjønstad *et al*, 2000; Helleve *et al*, 2010) and breast cancer incidence for Norwegian women (Cancer Registry of Norway, 2014).

We consider it a key strength that, in addition to the main focus of this paper, we were able to address six (dose response for different measures of smoking exposures, smoking at an early age or before first pregnancy, a no active/no passive exposure reference group, the extent to which the use of alcohol confounds the association between smoking and risk of breast cancer, the risk according to menopausal status, and the risk according to estrogen hormone receptor status) of the seven questions listed in the Surgeon General's report (US Department of Health and Human

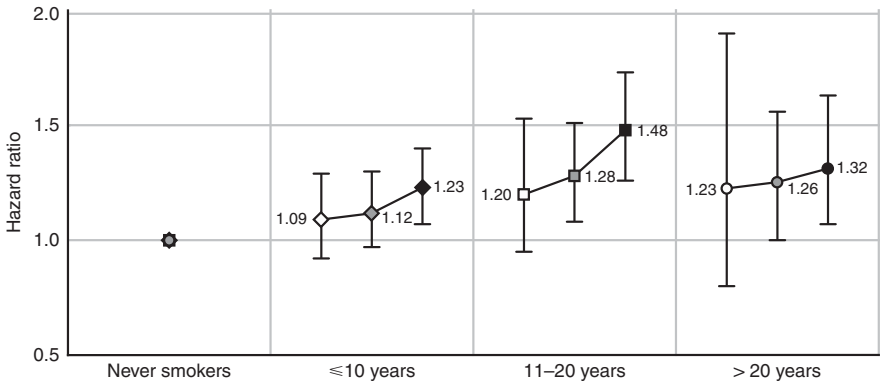

Figure 1. Multivariate[a] adjusted hazard ratio estimates with 95% confidence intervals for breast cancer among parous women according to total (⩽10, 11–20, >20) years of smoking and smoking initiation in relation to first birth for ever compared with never (excluding passive) parous smokers, Norwegian Women and Cancer study 1991–2012. ◇, □, ○ Smoking initiation after first birth (white shapes). ◈, ■, ● Smoking initiation <5 years before first birth (grey shapes). ♦, ■, ● Smoking initiation 5 or more years before first birth (black shapes). [a]Co-variates included in the multivariate model were age, duration of education, hormone therapy, age at menarche, family history of breast cancer, age at first birth, number of children, hormonal contraceptive use, menopausal status, alcohol consumption and BMI, all at enrolment.

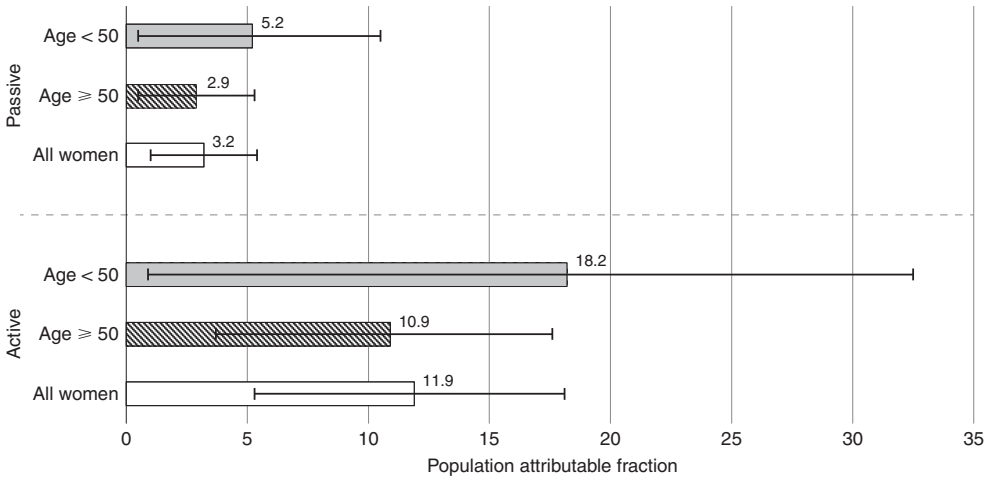

Figure 2. The fraction of breast cancer (%) attributable to passive and active (ever) smoking in middle-aged women in Norway in 2012. The Norwegian Women and Cancer study 1991–2012. Grey-shaded boxes, women <50 years at diagnosis. Marked boxes, women 50 years or more at diagnosis. White boxes, all women.

Services, 2014). Another strength is that, in our analyses, we have addressed the previously described main concern about confounding by alcohol consumption (International Agency for Research on Cancer, 2012; US Department of Health and Human Services, 2014). Our results support the notion that the association between smoking and breast cancer is not confounded by alcohol. We have previously shown this in both the European cohort study (Dossus *et al*, 2014) with close to 10 000 breast cancer cases and in the US cohort study (Gram *et al*, 2015) with more than 4000 breast cancer cases.

Another important contribution of this paper is that our results show that the increase in risk almost disappear when we include the passive smokers in the reference group. This finding helps explain the 'negative' or 'null' results in most of the older studies (California Environmental Protection Agency, 2005; Collishaw *et al*, 2009; Johnson *et al*, 2011; International Agency for Research on Cancer, 2012; US Department of Health and Human Services, 2014). Also, the corresponding PAF value decreases from almost 12% to <5% of the breast cancer cases that could have been avoided in the absence of smoking.

Other major strengths are the virtually complete follow-up through the National population-based registries, our ability to control for potential confounders, the high proportion of ever smokers, the 30-year lag period between smoking initiation and time of cohort enrolment for the majority of smokers. We focus our estimates on ever *vs* never smokers, which means that the women do not change smoking status during follow-up. In Norway, very few women initiate smoking after our enrolment age of 35 years (Gram *et al*, 2005; Helleve *et al*, 2010; Bjerkaas *et al*, 2013).

We also consider it a strength that we have a high proportion (i.e., more than 65%), ever smokers. The corresponding figure for the other recently published cohort studies was 59% for the large Norwegian (Bjerkaas *et al*, 2013) study, 55% for the US (Nyante *et al*, 2014) study, around 44% for three of the studies; the Canadian (Catsburg *et al*, 2015), the Multi-Ethnic Cohort (Gram *et al*, 2015), and the EPIC (Dossus *et al*, 2014) study, and 37% for the African American (Rosenberg *et al*, 2013) study.

The main limitation of the present study is the fact that despite more than 4000 incident cases of breast cancer, the numbers of

cases were small for important subset analyses, for example after stratification for both years of smoking and years of smoking before first childbirth among parous women. In addition, when we do separate analyses for women diagnosed before age 50, we get wide CIs for the PAF estimates due to few cases. Also, we have very crude estimates for passive smoking and we did not assess lifetime drinking patterns. We find it difficult to predict what impact more detailed information on these two variables would have had on our results. Furthermore, with longer follow-ups the increased breast cancer risk among ever compared with never smokers may be concealed or obscured by censoring due to other smoking-related cancers (Gram *et al*, 2008, 2009; International Agency for Research on Cancer, 2012) and competing causes of death (Gram *et al*, 2013). There may be some residual confounding due to the above-described factors, or other factors we did not measure. However, we find it unlikely that these associations should be of a magnitude that would change our PAF results materially.

In conclusion, our findings support the notion that the global cancer burden due to smoking is substantially underestimated. Our results emphasise the need to increase the global effort to stop the tobacco industry recruiting teenage girls to smoke. Our study shows that the number of breast cancer cases that may be prevented worldwide is huge.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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