Social inequalities and smoking-associated breast cancer — Results from a prospective cohort study

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ABSTRACT

Objective. The association between smoking and breast cancer has been found in most recent, large cohort studies. We wanted to investigate how smoking-associated breast cancer varies by level of education, a well-established measure of socioeconomic status.

Methods. We included 302,865 women with 7490 breast cancer cases. Participants were assigned to low, moderate or high level of education and analyzed by smoking status (ever/never), and stratified by birth cohorts ($\leq 1950>$). We used Cox proportional hazard to estimate hazard ratios (HRs) and confidence intervals (CIs), adjusting for age, number of children, age at first childbirth, BMI, age at enrollment and physical activity.

Results. Women born ≤ 1950 with low and moderate levels of education had a 40% increase in smoking-associated breast cancer risk (HR = 1.40, 95% CI 1.25–1.57 and HR = 1.14, 95% CI 1.05–1.24, respectively). Women in the same age group with high level of education did not have an increase in risk. No increased breast cancer risk was found among women born after 1950 for any level of education, when analyzed by smoking status. Longer duration of smoking before first childbirth was consistently associated with increasing risk of breast cancer in all three categories of education (all p for trends < 0.01).

Conclusion. Smoking for several years before first childbirth increases the risk of breast cancer, regardless of educational level.

Introduction

Socioeconomic differences in risk factors have been reported for many diseases, including breast cancer (International Agency for Research on Cancer, 1997; Mackenbach et al., 2008; Menvielle et al., 2009). Socioeconomic status (SES), often measured as educational achievement (Carter et al., 1989; Braaten et al., 2004; Pukkala et al., 2009), acts as an indicator for etiologically relevant risk factors (Braaten et al., 2004), and most studies find more breast cancer in women with high SES (International Agency for Research on Cancer, 1997; Dano et al., 2003; Braaten et al., 2005). The association between smoking and breast cancer is still under debate (Johnson et al., 2011; IARC. International Agency for Research on Cancer, 2012; U.S.Department of Health and Human Services, 2014). However, most recent, well conducted cohort studies of this relationship are relatively consistent with a 5–32% higher risk for current, and a 5–18% higher risk for former smokers, compared with never smokers (Reynolds et al., 2004; Nyante et al., 2014; Gram et al., 2005; Olson et al., 2005; Cui et al., 2006; Ha et al., 2007; Luo et al., 2011; Xue et al., 2011; DeRoo et al., 2011; Bjerkaas et al., 2013; Gaudet et al., 2013; Rosenberg et al., 2013; Dossus et al., 2014).

After the introduction of tobacco products more than 100 years ago (Graham, 1996), smoking was more common in groups with high SES (Norges offentlige utredninger, 2000). This situation changed gradually during the 1960s when smoking became more widespread in groups with low SES. Today we find a higher smoking prevalence in women with low SES; they are using more harmful smoking products, have an earlier age at smoking initiation, and have a lesser degree of smoking cessation, than women with high SES (Norwegian Institute of Public Health, 2014). As a consequence, smoking contributes to socioeconomic inequalities in health (Kulik et al., 2014; Graham, 2009).

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As more evidence points towards a positive association between smoking and breast cancer, it is interesting to examine how this association may affect socioeconomic inequalities. In this paper we present results from a large Norwegian cohort with a high number of smokers, and with complete information on educational achievement from official statistics. The aim was to investigate how smoking-associated breast cancer varies by educational achievement, a well-established measure of SES (Carter et al., 1989; Braaten et al., 2004; Pukkala et al., 2009).

Methods

Study population

The study population has been previously described (Bjerkaas et al., 2013; Naess et al., 2008; Bjerkaas et al., 2014; Bjartveit et al., 1979), and comprises three national Norwegian health studies conducted in between 1974 and 2003 by the Norwegian National Health Screening Service. Overall, 330,342 women were eligible and 302,865 remained in the analytical cohort after exclusions due to emigrations or death prior to study enrollment (n = 3933), prevalent cancer (n = 7138), or due to missing information on covariates included in the analyses (n = 16,406). Selection of participants was based on the year of birth and residence (municipality or county). The response rate in the three studies varied from 56% to 88% (Stocks et al., 2010). The design and protocol of the three studies were similar, though some modifications regarding smoking, level of physical activity and other lifestyle factors were made in the questionnaires at different time periods. The present study was approved by the Regional Committee for Medical Research Ethics South-East, Norway.

Exposure information

All baseline questionnaires included a detailed assessment of smoking habits, though the questions related to smoking varied across studies. Current and former smokers were considered ever smokers, whereas all other participants were classified as never smokers. For parous women, the variable "smoking duration before first childbirth" was calculated in years as age at smoking initiation or duration of smoking in years, subtracted from age at first childbirth. To control for birth cohort effects (Korn et al., 1997), we displayed the results by birth cohorts ($\leq$1950 and >1950). Based on information from the questionnaires, physical activity was categorized into three groups: low physical activity (reading, watching television, and sedentary activity), moderate physical activity (walking, bicycling, or similar activities $\geq$4 h per week), and heavy physical activity (light sports or heavy gardening $\geq$4 h per week, heavy exercise or daily competitive sports). The most recent information regarding duration of education obtained from Statistics Norway was used to assign participants to one of the three categories according to the duration of education: low (<10 years), moderate (10–12 years), and high (>12 years). Fifty years of age was used as a proxy measure of menopausal status, considering women diagnosed with breast cancer before age 50 as premenopausal breast cancer, and diagnosed after age 50 as postmenopausal breast cancer. Information on alcohol consumption was either not collected or missing in 62% of the women in the analytical cohort and was not used in our main analysis. Participants were followed through record linkages with the virtually complete official registries (Larsen et al., 2009) using the unique 11-digit personal identification number to identify all invasive breast cancer cases, deaths and emigrations. The start of follow-up was set to January 1 the year following completion of the baseline questionnaire. The Seventh Revision of the International Classification of Diseases (ICD-7 code 170) was used to identify breast cancer cases in the Cancer Registry.

Statistical analysis

We used Cox proportional hazard models (with age as the underlying time scale) to estimate the multivariate-adjusted hazard ratios (HRs) for breast cancer with 95% confidence intervals (CIs). The start of the follow-up was defined as age at enrollment, and exit time as age at breast cancer diagnosis, the date of any other incident cancer diagnosis (except basal cell carcinoma), emigration, deaths or the end of follow-up (31 December 2007), whichever occurred first. The covariates included in the final models were selected a priori based on previously performed analysis in the assessment of breast cancer risk by smoking status (Braaten et al., 2004; Key et al., 2001; IARC International Agency for Resrach on Cancer, 2014), and were age at enrollment (continuous variable), number of children (0, 1–2, 3–4, $\geq$5), age at first childbirth (<20, 20–24, 25–29, $\geq$30 years), BMI (<25, 25–29, $\geq$30 kg/m^2) and level of physical activity (sedentary, moderate, heavy). The reference groups were never smokers in each level of education category (low, moderate, high). We also stratified the models according to selected covariates and performed tests for linear trends across levels of exposure. The Wald's test was used for testing interaction. The results were considered significant if the p value was < 0.05. All p values are two sided. The analyses were performed in STATA version 12.0 (StataCorp, College Station, TX, USA) and in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

We confirmed 7490 cases of breast cancer during 4.1 million person years and 14 years of median follow-up. For women born >1950, 78% of those with a lower and 44% with a higher education were smokers. For women born $\leq$1950 the corresponding figures were 60% and 42%. Age at first childbirth for ever smokers was 21 years for women with low education and 27 years for women with high education when born >1950 (Table 1).

Table 2 shows that compared with women with low level of education, the breast cancer risk increases for women with increasing years of education, overall and stratified by birth cohort (all p for trends <0.01). For women born $\leq$1950, those with a higher education had a 62% increased breast cancer risk (HR = 1.62, 95% CI 1.48–1.76) as compared with those with a low level of education.

Table 3 shows the risk of breast cancer stratified by level of education among ever compared to never smokers according to birth cohort and menopausal status at diagnosis, for different measures of smoking exposures at enrollment, with never smokers as reference. Women with a high level of education did not have a significantly increased risk in any of the two birth cohorts when ever smokers were compared with never smokers. For women born $\leq$1950, ever smokers had a significantly increased breast cancer risk of 40% (HR = 1.40, 95% CI 1.25–1.57) among those with lower and of 14% (HR = 1.14, 95% CI 1.05–1.24) among those with moderate education compared with never smokers. The test for interaction between low and high levels of education showed a significant difference in the oldest birth cohort (p Wald < 0.01). The analysis for menopausal status at diagnosis and birth cohorts displayed a significant difference between the birth cohorts for postmenopausal breast cancer and low (p Wald = 0.03) but not for high level (p Wald = 0.05) of education.

For women with low education, a significant test for trend was revealed for all five (age at smoking initiation, smoking duration, number of cigarettes smoked per day, number of pack years and duration of smoking in relationship to first childbirth) measures of smoking exposure displayed in the table (all p values < 0.03).

Compared with parous never smokers, women who had smoked seven or more years before their first childbirth had a significantly increased risk of breast cancer for all three [low (HR = 1.70, 95% CI 1.40–2.08); moderate (HR = 1.38, 95% CI 1.24–1.55) and high (HR = 1.37, 95% CI 1.17–1.60)] level of education. Longer duration of smoking before first childbirth was associated with increasing risk of breast cancer in all three categories of education (all p for trends < 0.01).

Discussion

This study presents the first results of a differential risk between smoking-associated breast cancer and education, a measure of socioeconomic status (SES). Our analysis shows that the incidence of breast cancer increases with higher level of education, in accordance with the results of other studies (Braaten et al., 2004; Dano et al., 2003; Braaten et al., 2005; Hussain et al., 2008). In contrast, the incidence of smoking-associated breast cancer is not increased in women with high level of education when the analyses are done by smoking status, with never smokers as reference. Also, we find increasing risk with

Table 1

Study population characteristics, stratified by level of education (low, moderate, high), birth cohort (≤1950>) and smoking status (ever/never), among 302,865 Norwegian women (1974–2003).

Level of education	Low (Less than 10 years)				Moderate (10–12 years)				High (More than 12 years)				All		
Birth cohort (year of birth)	≤1950		>1950		≤1950		>1950		≤1950		>1950		≤1950	>1950	Total
Characteristics/smoking status ▸	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	
Subjects	27,856	18,291	22,097	6,266	36,341	28,612	66,344	35,303	8,445	11,491	18,279	23,540	149270	153595	302,865
Age (mean)	47	53	41	39	45	48	41	40	46	46	42	41	47	41	44
Number of primary invasive breast cancers	966	502	315	81	1477	1052	959	499	403	509	342	385	4909	2581	7,490
Age at diagnosis, (mean) SD	57 ± 9	63 ± 12	49 ± 4	49 ± 4	55 ± 8	57 ± 9	48 ± 4	48 ± 4	55 ± 7	55 ± 8	48 ± 4	48 ± 4	57 ± 9	48 ± 4	54 ± 9
Follow-up years, (median)	17	17	11	11	17	17	10	10	17	17	10	10	16	10	14
Number of children, (mean), SD	2 ± 2	3 ± 2	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 1	2 1	2 ± 1
Age at first childbirth, (mean), SD	22 ± 4	24 ± 5	21 ± 4	22 ± 4	23 ± 4	24 ± 4	24 ± 4	24 ± 4	26 ± 4	27 ± 4	27 ± 5	27 ± 4	24 4	24 5	24 ± 5
Age at smoking initiation (year), SD	22 ± 7	NA	18 ± 4	NA	22 ± 6	NA	18 ± 4	NA	23 ± 6	NA	19 ± 5	NA	22 6	18 4	20 ± 6
BMI (kg/m^2)	25	27	25	26	24	25	24	25	24	24	24	24	25	25	25
Heavy level of physical activity %	8	6	21	25	11	12	27	29	15	15	34	34	11	31	21
Smoking status %	60	40	78	22	56	44	65	35	42	58	44	66	61	58	59

Ever smoker: current and former smoker. A former smokers has been a daily smoker previously.

a = At enrollment.

b = Information not available for all smokers.

c = Heavy level of physical activity: light sports or heavy gardening >4 h per week, heavy exercise or daily competitive sports.

d = 59% ever smokers at enrollment.

SD = Standard deviation.

NA = Not applicable.

increasing smoking exposure in most categories, most consistent in women with low education.

Our findings are supported by the results from four, recent large cohort studies on smoking and breast cancer, showing the highest risks among women who smoke the most before their first childbirth (Bjerkaas et al., 2013; Gaudet et al., 2013; Rosenberg et al., 2013; Dossus et al., 2014).

It is unclear why women with low level of education, born in and before 1950, have a significantly higher risk for smoking-associated breast cancer than women with high level of education in the same category. Smoking may have a stronger impact on breast cancer risk in these women, possibly reducing the importance of other known risk factors. In the recent study from the large EPIC cohort, Dossus et al. (2014) demonstrate a significantly higher breast cancer risk among current smokers with low versus with high educational level (21% vs 12%, respectively). The majority of the included women in this cohort were born before 1950, supporting our observation of an increased smoking-associated risk among current smokers with low educational achievement in this age group. To our knowledge, other studies have not evaluated the association between breast cancer, smoking and level of education in detail, as in the present study.

Table 2

Multivariate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer, according to levels of education, with low level of education as the reference group. From a Norwegian pooled cohort (1974–2003).

Birth Cohort		All	≤1950	>1950
		n = 302865	149270 (49%)	153595 (51%)
Level of education (in years)	Cases/n			
Low (<10)	1864/74510	Ref.	Ref.	Ref.
Moderate (10–12)	3987/166600	1.27 (1.20–1.35)	1.32 (1.23–1.41)	1.04 (0.93–1.17)
High (≥13)	1639/61755	1.53 (1.43–1.64)	1.62 (1.48–1.76)	1.18 (1.04–1.34)
Trend test[a]		p < 0.01[a,b]	p < 0.01[a,b]	p < 0.01[a,b]

Adjusted for age, number of children, age at first childbirth, BMI, age at enrollment and physical activity.

[a] Trend test between the three levels of education.

[b] Significant p < 0.05.

We also find a non-significant risk increase in women with high level of education in both birth cohorts; i.e. never and ever smokers with high level of education have a similar breast cancer risk, when analyzed by smoking status. This observation indicates that smoking has a limited impact on women with higher education, for the association with breast cancer. In the study by Braaten et al. (2004), the association between breast cancer and education was fully explained by the following breast cancer risk factors: low parity, higher age at first childbirth, lower BMI, increased height, lower age at menarche, later age at menopause, more frequent alcohol consumption and use of oral contraceptives. Smoking was not included as a covariate in the Braaten study, and the present analysis supports the notion that smoking is not a mandatory covariate when explaining the educational inequalities in the association for smoking and breast cancer.

Further, the analysis for the different smoking exposures (age at smoking initiation, smoking duration, number of cigarettes smoked per day, pack-years and smoking duration before first childbirth) mostly showed increasing breast cancer risk with increasing smoking exposure. In particular, the results for women with low level of education revealed a significant trend in all categories. Recent literature shows the importance of analyzing smoking and breast cancer association with increasing smoking exposures, not only by smoking status (ever, current, former, never), to promote the importance of dose-response. Our results for smoking duration before first childbirth show an increasing risk with increasing duration of smoking for all levels of education, supporting the notion that smoking in this time period is an important risk factor for breast cancer.

Strengths and limitations

The strengths of this study include the large number of enrolled women representing all counties in Norway, the long follow-up, the large number of breast cancer cases, the valid information about level of education and the excellent follow-up information through official Norwegian Statistics. The large size makes it possible to stratify for education and different smoking exposures including smoking initiation before first childbirth. In our analysis, we stratified the study sample by two birth cohorts, as the reproductive and lifestyle behavior have changed over time during the follow-up. The level of education,

Table 3

Multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer according to level of education and different measures of smoking exposures at enrollment, with never smokers as the reference group. From a Norwegian pooled cohort (1974–2003).

			Level of education							
			Low		Moderate		High		All	
			Cases	HR	Cases	HR	Cases	HR	Cases	HR
Birth cohort	≤1950		1468	1.40 (1.25–1.57)	2529	1.14 (1.05–1.24)	912	1.10 (0.96–1.25)	4909	1.15 (1.08–1.21)
	>1950		369	0.97 (0.76–1.25)	1458	0.97 (0.87–1.08)	727	1.12 (0.97–1.30)	2581	0.98 (0.91–1.07)
		p Wald[a]		<0.01[a,b]		0.02[a,b]		0.86[a]		<0.01[a]
Premenopausal at diagnosis (a)	≤1950		310	0.90 (0.69–1.16)	757	1.03 (0.89–1.20)	266	0.84 (0.65–1.08)	1333	0.97 (0.87–1.09)
	>1950		256	1.19 (0.86–1.65)	1043	0.92 (0.81–1.05)	520	1.02 (0.85–1.21)	1819	0.99 (0.90–1.09)
		p Wald[a]		0.05[a]		0.25[a]		0.20[a]		0.77[a]
Postmenopausal at diagnosis (a)	≤1950		1158	1.42 (1.25–1.61)	1772	1.14 (1.03–1.25)	646	1.13 (0.97–1.32)	3576	1.21 (1.13–1.30)
	>1950		140	0.94 (0.63–1.42)	415	0.96 (0.78–1.17)	207	1.17 (0.89–1.54)	762	1.01 (0.87–1.18)
		p Wald[a]		0.03[a,b]		0.11[a]		0.83[a]		0.02[a,b]
Smoking exposures:										
Age at smoking initiation	≥25		213	1.11 (0.94–1.29)	312	0.93 (0.82–1.05)	106	0.99 (0.81–1.22)	631	0.98 (0.90–1.07)
	20 to 24		325	1.38 (1.20–1.59)	626	1.11 (1.01–1.21)	176	1.08 (0.92–1.27)	1127	1.16 (1.08–1.24)
	<20		489	1.54 (1.35–1.76)	917	1.17 (1.07–1.27)	199	1.23 (1.05–1.43)	1605	1.26 (1.18–1.34)
		p trend[c]		p = 0.02[b,c]		p = 0.69[c]		p = 0.39[c]		p = 0.04[b,c]
Smoking duration (years) (b)	<11		238	1.18 (1.01–1.38)	614	1.02 (0.93–1.12)	306	1.14 (1.00–1.29)	1158	1.08 (1.02–1.15)
	11 to 20		503	1.27 (1.12–1.43)	1022	1.08 (1.00–1.17)	297	1.08 (0.95–1.24)	1822	1.12 (1.05–1.35)
	>20		527	1.54 (1.36–1.74)	781	1.17 (1.07–1.28)	136	1.14 (0.95–1.37)	1444	1.27 (1.19–1.35)
		p trend[c]		p < 0.01[b,c]		p < 0.01[b,c]		p = 0.06[c]		p < 0.01[b,c]
Number of cigarettes smoked per day	<6		204	1.31 (1.12–1.54)	413	1.03 (0.92–1.15)	169	1.00 (0.85–1.18)	786	1.08 (0.99–1.17)
	6 to 15		874	1.33 (1.19–1.48)	1625	1.09 (1.02–1.17)	432	1.11 (0.99–1.24)	2931	1.15 (1.09–1.21)
	>15		197	1.57 (1.33–1.86)	388	1.19 (1.06–1.33)	140	1.34 (1.12–1.60)	725	1.30 (1.20–1.41)
		p trend[c]		p < 0.01[b,c]		p < 0.01[b,c]		p < 0.01[b,c]		p < 0.01[b,c]
Number of pack-years	<6		341	1.20 (1.04–1.38)	777	1.04 (0.94–1.13)	319	1.03 (0.90–1.17)	1437	1.07 (1.00–1.14)
	6 to 15		614	1.28 (1.14–1.44)	1134	1.07 (0.99–1.16)	319	1.19 (1.04–1.36)	2067	1.14 (1.07–1.21)
	>15		350	1.71 (1.49–1.97)	555	1.24 (1.12–1.36)	116	1.19 (0.98–1.46)	1021	1.35 (1.25–1.45)
		p trend[c]		p < 0.01[b,c]		p < 0.01[b,c]		p < 0.01[b,c]		p < 0.01[b,c]
Smoking initiation in relation to first childbirth for parous women (years)										
After first childbirth (>1 year)			231	1.12 (0.96–1.30)	309	0.90 (0.82–1.08)	49	0.76 (0.57–1.01)	589	0.93 (0.86–1.02)
Around first childbirth (d)			198	1.51 (1.28–1.78)	244	0.95 (0.82–1.08)	40	0.94 (0.68–1.29)	482	1.09 (0.99–1.20)
1–6 years before first childbirth			339	1.42 (1.24–1.64)	646	1.11 (1.01–1.22)	127	1.08 (0.89–1.30)	1112	1.17 (1.10–1.26)
≥7 years before first childbirth			137	1.70 (1.40–2.08)	439	1.38 (1.24–1.55)	204	1.37 (1.17–1.60)	780	1.44 (1.32–1.56)
		p trend[d]		p < 0.01[b]		p < 0.01[b]		p < 0.01[b]		p < 0.01[b]

Adjusted for age, number of children, age at first childbirth, BMI, age at enrollment and physical activity.
(a) Premenopausal if diagnosis at ≤50 years of age, postmenopausal if diagnosis >50 years of age.
(b) Total number of years smoked.
(d) 1 year before to 1 year after first childbirth.
[a] Wald test for interaction.
[b] Significant p < 0.05.
[c] Trend test between three levels of smoking categories excluding never smokers.
[d] Trend test between three levels of smoking categories excluding never smokers, and excluding those smoking after first childbirth.

however, is not based on information at baseline, but comes from individual information from Statistics Norway, and measures the highest lifetime level of education achieved during the study period. Further, our smoking exposure analyses were based on the comparison between ever and never smokers, and as only never smokers could change their smoking status during follow-up, the chance of misclassification in smoking status in the follow-up period is significantly reduced. However, the long study period without follow-up information limits our opportunity to make causal conclusions. Educational achievement is considered to be a robust measure of SES, as it applies to every adult individual, is more stable throughout life than occupation or income, and is easily obtainable and recordable (Carter et al., 1989; Braaten et al., 2004; Pukkala et al., 2009). The limitations include lack of information for established risk factors for breast cancer such as age at menopause and menarche, use of oral contraceptives and hormonal replacement therapy (HRT). The use of HRT became more widespread after 1990 (Bakken et al., 2004), and may be a more important limitation in the younger birth cohort. The higher use of HRT in more educated groups may also have biased the associations by SES. Heavy smoking and higher SES is associated with high alcohol consumption (Bobo and Husten, 2000; Strand and Steiro, 2003), while smoking in the recent decades has been associated with lower SES. We consider the lack of information on alcohol consumption as an important limitation of this study,

and the level of confounding is uncertain. A difference in follow-up time between the birth cohorts may partly explain the difference in incidence between the birth cohorts, and limits our ability to conclude of a birth cohort difference.

The relative distribution of women with high level of education in Norway has increased substantially the past decades, from less than 10% in 1980 to more than 26% in 2013 (Statistics Norway, 2013). An increasing proportion of women in Norway will have high level of education in the future, adapting underlying breast cancer risk factors, increasing their risk for breast cancer in general. The past reductions in smoking prevalence among women in Norway will in the future reduce the incidence of smoking-associated diseases, which according to most recent studies (Reynolds et al., 2004; Nyante et al., 2014; Gram et al., 2005; Olson et al., 2005; Cui et al., 2006; Ha et al., 2007; Luo et al., 2011; Xue et al., 2011; DeRoo et al., 2011; Bjerkaas et al., 2013; Gaudet et al., 2013; Rosenberg et al., 2013; Dossus et al., 2014), includes breast cancer.

Conclusions

Smoking for several years before first childbirth increases the risk of breast cancer, regardless of educational level. More studies are

warranted explaining how smoking-associated breast cancer varies by educational achievement.

Conflict of interest statement

None conflicts of interest.

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