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Short Communication

Breast cancer and ductal carcinoma *in situ* among women with prior squamous or glandular precancer in the cervix: a register-based study

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BACKGROUND: Human papillomavirus and hormonal contraceptives may be risk factors for cervical precancer and malignant breast tumours.

METHODS: Standardised incidence ratios (SIRs) of malignant breast tumours during 1970–2008 were estimated separately for women with prior squamous and glandular cervical precancer.

RESULTS: Women with squamous precancer and women with glandular precancer in the cervix had a significantly higher risk of malignant breast tumours than the general female population (SIR, 95% confidence interval: 1.10, 1.05–1.14 and 1.52, 1.11–2.08, respectively).

INTERPRETATION: Shared risk factors or screening attendance may explain the excess risk of malignant breast tumours among women with a history of cervical precancer.

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Clinical Studies

Cervical human papillomavirus (HPV) infection is sexually transmitted and is cleared without treatment in most cases (Rodriguez *et al*, 2008). However, under certain conditions, HPV infections persist and can induce cervical precancer and cancer (Bosch and de Sanjose, 2003), which may occur in squamous or glandular tissue.

A causal relationship between HPV and breast cancer has been suggested (Amarante and Watanabe, 2009), and a review of 20 studies shows that nearly a quarter of breast carcinomas tested for HPV were HPV-positive (Li *et al*, 2011). Hormonal contraceptive use may also increase the risk of both cervical precancer (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007) and breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Although cervical precancer and breast cancer may share risk factors, women with cervical precancer do not appear to suffer an increased risk of breast cancer (Bjorge *et al*, 1995; Jakobsson *et al*, 2011). However, no study has separately investigated the risk of breast cancer among women with glandular cervical precancer.

We aim to investigate the risk of malignant breast tumours among women with prior squamous or glandular cervical precancer in separate analyses.

MATERIALS AND METHODS

Data were collected from the Cancer Registry of Norway (CRN), which has a near-complete registration of cancer in Norway from 1953 onwards (Larsen *et al*, 2009). Registration of precancer and cancer is mandated by Norwegian law, and patients are identifiable in the CRN by a personal identification number. We used de-identified data, which are publically available for research upon application to the CRN. Norway implemented organised cervical cancer screening in 1995. The program reminds women aged 25–69 years to have a cytological smear every third year. Organised breast cancer screening was implemented in Norway during 1995–2005. The program invites women aged 50–69 years to mammography biennially. Information about ductal carcinoma *in situ* (DCIS) is available at the CRN from 1993 onwards.

We used DCIS or breast cancer as a combined disease end point, that is, DCIS or worse (hereafter, DCIS+). If a woman was registered with several malignant breast diagnoses simultaneously (within 4 months), we used the diagnosis with the highest stage. Localised tumours were defined as DCIS and invasive breast cancer stage 1, and metastatic tumours were defined as cancer stages 2–4. In analyses of localised and metastatic tumours, cases with unknown stage were excluded.

Women with a histologically confirmed cervical precancer diagnosis during 1970–2007, and no history of DCIS+ prior to the cervical precancer diagnosis, were included in the study cohorts. They entered the study at the date of their first squamous or glandular cervical precancer diagnosis, and were followed up during 1970–2008, until the date of their first diagnosis of DCIS+, emigration, death or 31 December 2008, whichever occurred first. Risk of DCIS+ was analysed separately for women diagnosed with glandular and squamous cervical precancer. The cohort with squamous precancer (hereafter, the cervical intraepithelial neoplasia (CIN) cohort) consisted of women with high-grade CIN or Bowen's disease (ICD-O-3 codes: 8070/1, 8070/2, 8077/1, 8077/2 and 8081/2). The cohort with glandular precancer (hereafter, the

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adenocarcinoma *in situ* (AIS) cohort) consisted of women with AIS or moderate/severe glandular/glandulosquamous dysplasia (ICD-O-3 codes: 8140/1, 8140/2 and 8560/2). Women with both squamous and glandular cervical precancer diagnoses were included in both cohorts from the date of their first squamous and glandular diagnosis, respectively.

The expected number of malignant breast tumour cases was calculated by multiplying the age- and period-specific incidence rate for the Norwegian female population with the observed number of woman-years at risk in the cohort. We calculated the standardised incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs), assuming Poisson-distributed data. All the tests were two-tailed, and *P*-values <0.05 were considered statistically significant. Means are given with ± 1 s.d.

RESULTS

A total of 87 285 women with a diagnosis of squamous cervical precancer were followed up for a mean of 15.7 (± 9.7) years. The mean age at first squamous cervical precancer diagnosis was 35.7 (± 11.2), and DCIS+ was subsequently diagnosed in 2054 of the women (171 with DCIS and 1883 with breast cancer) at mean age 54.4 (± 10.8). Most of the CIN cohort follow-up time was accumulated at ages 30–59, and in the period from 1990 onwards (Table 1). Few cases of DCIS+ were observed before age 30. Women in the CIN cohort had a significantly higher incidence of DCIS+ than the general female population (SIR 1.10, 95% CI: 1.05–1.14; Table 1). The SIRs for DCIS+ were similarly elevated for ages 30–79, but reached statistical significance only for ages 40–59. For women <30 and >79 years, no excess risk was detectable (Table 1). The SIRs for DCIS+ varied somewhat between decades, and 2000–2008 was the only calendar period with a significantly elevated SIR (Table 1). Women in the CIN cohort had a significantly elevated SIR for localised breast tumours (1.14, 1.08–1.21), but not for metastatic tumours (1.02, 0.96–1.09; Table 1).

A total of 1860 women with a diagnosis of glandular cervical precancer were followed up for a mean of 9.3 (± 7.0) years. Glandular cervical precancer was on average first diagnosed at age 40.3 (± 12.7). The DCIS+ was subsequently diagnosed in 39 women (2 with DCIS and 37 with breast cancer) at mean age 57.7 (± 12.7). Most of the AIS cohort follow-up time was accumulated at ages 30–59, and in the period from 1990 onwards (Table 2). No cases of DCIS+ were observed before age 30. Women in the AIS cohort had a significantly elevated SIR for DCIS+ (1.52, 1.11–2.08; Table 2). Restricting the analysis to women with a history of glandular cervical precancer only and no history of squamous cervical precancer ($N=923$) also gave a significantly elevated SIR for DCIS+ (1.76, 1.20–2.58). The SIRs for DCIS+ in the AIS cohort varied somewhat across age groups, but no consistent trend could be discerned (Table 2). Elevated SIRs for DCIS+ were observed after 1990, but not earlier (Table 2). The SIRs for localised (1.50, 0.98–2.31) and metastatic breast tumours (1.51, 0.95–2.40) were both elevated, but fell short of significance (Table 2).

DISCUSSION

In contrast to previous research (Bjorge *et al*, 1995; Levi *et al*, 1996; Hemminki *et al*, 2000; Evans *et al*, 2003; Kalliala *et al*, 2005; Jakobsson *et al*, 2011), we showed that women with prior cervical precancer had a higher incidence of malignant breast tumours compared with females in the general population. The present study cannot answer what caused the association. One potentially common risk factor for cancer at both sites is HPV. Acquisition of multiple HPV-related diseases may be associated, because women with cervical precancer suffer an increased risk of other HPV-related cancers (Edgren and Sparen, 2007). A similar scenario is controversial for breast cancer because detection of HPV in breast cancers has been inconsistent (Li *et al*, 2011), and the viral load in HPV-positive breast cancers is low (Khan *et al*, 2008; Herrera-Goepfert *et al*, 2011).

Human papillomavirus 18 is especially prevalent in AIS (Dahlstrom *et al*, 2010) and adeno-/adenosquamous carcinoma (Smith *et al*, 2007), and may hence have an affinity for glandular tissue. Most breast cancers are of glandular origin, and some studies indicate that HPV 18 may be relatively common in HPV-positive breast cancers (Heng *et al*, 2009; Antonsson *et al*, 2011; Li *et al*, 2011).

Table 1 SIRs for malignant breast tumours among women with a previous diagnosis of squamous cervical precancer

	Woman-years	Observed number of cases	Expected number of cases	SIR (95% CI)	*P*-value
DCIS+	1374461	2054	1873.65	1.10 (1.05–1.14)	<0.01
Age at diagnosis of DCIS+					
<20	1362	0	0.00	NA	NA
20–29	119671	5	3.76	1.33 (0.55–3.20)	0.52
30–39	389931	150	133.88	1.12 (0.95–1.31)	0.16
40–49	406093	602	545.08	1.10 (1.02–1.20)	0.01
50–59	269067	719	659.27	1.09 (1.01–1.17)	0.02
60–69	124534	402	369.45	1.09 (0.99–1.20)	0.09
70–79	50218	139	122.93	1.13 (0.96–1.34)	0.15
80+	13583	37	39.28	0.94 (0.68–1.30)	0.72
Period of diagnosis of DCIS+					
1970–79	57188	29	35.15	0.83 (0.57–1.19)	0.30
1980–89	226645	193	174.42	1.11 (0.96–1.27)	0.16
1990–99	465185	583	553.30	1.05 (0.97–1.14)	0.21
2000–08	625443	1249	1110.78	1.12 (1.06–1.19)	<0.01
Localised tumours[a]	1379352	1161	1016.44	1.14 (1.08–1.21)	<0.01
Metastatic tumours[b]	1382705	879	858.79	1.02 (0.96–1.09)	0.49

Abbreviations: CI = confidence interval; DCIS+ = ductal carcinoma *in situ* or invasive breast cancer; NA = not available; SIR = standardised incidence ratio. [a]Localised tumours = DCIS and invasive breast cancer stage 1. [b]Metastatic tumours = invasive breast cancer stages 2–4.

Table 2 SIRs for malignant breast tumours among women with a previous diagnosis of glandular cervical precancer

	Woman-years	Observed number of cases	Expected number of cases	SIR (95% CI)	*P*-value
DCIS+	17384	39	25.70	1.52 (1.11–2.08)	<0.01
Age at diagnosis of DCIS+					
<20	1	0	0.00	NA	NA
20–29	1160	0	0.04	NA	NA
30–39	4993	1	1.75	0.57 (0.08–4.06)	0.58
40–49	4723	10	6.58	1.52 (0.82–2.82)	0.19
50–59	3362	14	8.46	1.66 (0.98–2.79)	0.06
60–69	1870	5	5.60	0.89 (0.37–2.14)	0.80
70–79	930	8	2.27	3.52 (1.76–7.04)	<0.01
80+	345	1	0.99	1.01 (0.14–7.15)	0.99
Period of diagnosis of DCIS+					
1970–79	391	0	0.41	NA	NA
1980–89	1259	1	1.57	0.64 (0.09–4.53)	0.65
1990–99	4212	13	5.74	2.27 (1.32–3.90)	<0.01
2000–08	11522	25	17.99	1.39 (0.94–2.06)	0.10
Localised tumours[a]	17455	21	13.96	1.50 (0.98–2.31)	0.06
Metastatic tumours[b]	17562	18	11.89	1.51 (0.95–2.40)	0.08

Abbreviations: CI = confidence interval; DCIS+ = ductal carcinoma *in situ* or invasive breast cancer; NA = not available; SIR = standardised incidence ratio. [a]Localised tumours = DCIS and invasive breast cancer stage 1. [b]Metastatic tumours = invasive breast cancer stages 2–4.

We found that women with a history of glandular precancer had an increased risk of DCIS+, and that the risk was at least as high as that among women with squamous precancer. We have less data for women with glandular precancer than for women with squamous precancer because glandular precancer is less prevalent and more difficult to detect. This is a limitation of the present study.

Another common risk factor for breast cancer and cervical precancer/cancer may be the use of hormonal contraceptives (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). If women with cervical precancer have been more exposed to hormonal contraceptives than women in the general population, they could thus be at an increased risk of breast cancer. However, an effect of hormonal contraceptives on breast cancer risk is expected to occur primarily among relatively young women, which is not supported by our results.

Most of the follow-up time in our study was accrued after initiation of organised screening for breast cancer. Unfortunately, we do not have data to directly compare the screening attendance of women in the study cohorts and women in the general population. However, we separately calculated SIRs for localised and metastatic tumours, because localised tumours are more likely to be asymptomatic and thus are detected through screening. Among women with squamous precancer, an elevated SIR was found only for localised tumours. If women in the CIN cohort have been screened more for breast cancer than the general population, and screening to some extent leads to overdiagnosis of low-stage breast tumours (Zackrisson *et al*, 2006), it is possible that the elevated SIR found among women with squamous precancer reflects a difference in screening attendance rather than a difference in morbidity. Among women with glandular precancer, however, the SIRs for localised and metastatic tumours were similar.

This study takes advantage of registry data, which provides nearly complete follow-up of the study cohorts and precise information about all cervical precancer and malignant breast tumours diagnosed in Norway. In conclusion, we show that women with squamous and women with glandular cervical precancer suffer a slight, but significantly, increased risk of malignant breast tumours compared with the general female population.

Author contributions

BTH, MN, RSF and SH conceived and designed the study. BTH analysed the data and wrote the first draft of the manuscript. BTH, MN, RSF and SH revised several versions of the manuscript and approved the final draft.

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