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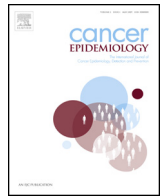
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Increased risk of colorectal cancer in patients diagnosed with breast cancer in women



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ABSTRACT

Background: Epidemiological studies have shown a potential association between sex hormones and colorectal cancer. The risk of colorectal cancer in breast cancer patients who may have been exposed to increased levels of endogenous sex hormones and/or exogenous sex hormones (e.g. anti-hormonal therapy) has not been thoroughly evaluated.

Methods: Using the National Swedish Cancer Register we established a population-based prospective cohort of breast cancer patients in women diagnosed in Sweden between 1961 and 2010. Subsequent colorectal cancers were identified from the same register. Standardized incidence ratios (SIRs) and 95% confidence intervals (95%CI) were used to estimate the risk of colorectal cancer after a diagnosis of breast cancer. The association between breast cancer therapy and risk of colorectal cancer was evaluated in a subcohort of breast cancer patients treated in Stockholm between 1977 and 2007. Hazard ratios (HRs) and 95%CI were estimated using Cox regression models.

Results: In a cohort of 179,733 breast cancer patients in Sweden, 2571 incident cases of colorectal cancer (1008 adenocarcinomas in the proximal colon, 590 in the distal colon and 808 in the rectum) were identified during an average follow-up of 9.68 years. An increased risk of colorectal adenocarcinoma was observed in the breast cancer cohort compared with that in the general population (SIR = 1.59, 95%CI: 1.53, 1.65). Adenocarcinoma in the proximal colon showed a non-significantly higher SIR (1.72, 95%CI: 1.61, 1.82) compared with the distal colon (1.46, 95%CI: 1.34, 1.58). In the subcohort of 20,171 breast cancers with available treatment data, 299 cases with colorectal cancers were identified. No treatment-dependent risk of colorectal cancer was observed among the breast cancer patients.

Conclusion: An increased risk of colorectal adenocarcinoma – especially in the proximal colon – was observed in the breast cancer cohort. Breast cancer treatment did not alter this risk.

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1. Introduction

Colorectal cancer is the most frequent neoplasia of the intestine. It is third in the list of most common cancers in men and second in women in developed countries [1]. For several decades, the incidence and mortality rates of colorectal cancer have exhibited persistent gender differences throughout the world [1,2]. Reproductive factors – including parity, oral contraceptive use, and hormone replacement therapy (HRT) – are associated with risk of breast cancer and are simultaneously known risk factors for colorectal cancer. Specifically, female predominance and

a diagnosis at old age have been observed in proximal colon cancer cases, while men have demonstrated a predominance of distal colon cancer. This evidence suggests that sex hormones may play a role in the pathogenic pathways of colorectal cancer and via subtypes, but whether this role is protective or not is controversial [3–10]. Interestingly, some studies have found positive associations between endogenous hormones and risk of colorectal adenocarcinoma [11,12]. There is, therefore, a need to clarify the role of exogenous and endogenous sex hormone levels on the risk of colorectal adenocarcinoma.

Breast cancer patients are characterized by high levels of endogenous estrogens [13,14]. However, only about 18% of these patients are below 50 years of age, and most breast cancers are diagnosed in women who are postmenopausal. It is uncertain whether a risk of colorectal cancer is increased after a diagnosis of breast cancer compared with that in the general population.

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Moreover, breast cancer treatment includes anti-hormone treatment (e.g., tamoxifen or aromatase inhibitors) which may influence sex hormone levels and further contribute to a risk of developing colorectal cancer. Several studies have explored the risk of colorectal cancer after a breast cancer diagnosis and treatment, and the results have been inconsistent [15–22].

We therefore established a nationwide breast cancer cohort from the Swedish Cancer Register to estimate the risk of colorectal cancer among breast cancer patients. In addition, we retrieved treatment information from the Stockholm–Gotland Breast Cancer Register which could further increase our understanding of how breast cancer treatment, including anti-hormone treatment, influences the risk of colorectal cancer.

2. Methods

2.1. Population and study design

Two cohorts were initiated in this study. The first, named the Total Breast Cancer Cohort (the TBC cohort), included all primary breast cancers in women identified from the Swedish Cancer Register during the period January 1st, 1961 to December 31st, 2010. If another cancer had been diagnosed before the breast cancer, the subject was excluded from the cohort. In total 179,733 breast cancer patients were included in the TBC cohort. The second cohort was retrieved from the Stockholm–Gotland Breast Cancer Register and named the SGBC cohort. It included breast cancer cases in women with relevant treatment information between 1977 and 2007. Only primary breast cancer patients between the ages of 15 and 75 years who had undergone surgery for breast cancer were included in the second cohort.

The two cohorts were followed up to the first occurrence of colorectal cancer (adenocarcinoma) as documented in the Swedish Cancer Register. The personal identity number, a unique 10-digit code assigned to each Swedish resident, was used for accurate individual linkage between registers. The study was approved by the Regional Ethical Review Board in Stockholm (DNR 2013/242–31/4).

2.2. Data sources

2.2.1. The Swedish cancer register

The breast cancer cohort was identified by the International Classification of Diseases, 7th edition (ICD-7: 170), from the Swedish Cancer Register (established in 1958). The register includes the date of diagnosis, tumor site (translated into ICD-7 codes), and histological type of all malignant tumors diagnosed in Sweden since 1958. Physicians and pathologists are obliged to report every cancer case, and the register has a minimum 96% nationwide completeness rate [23]. In order to exclude any potential influence of the prevalent malignancy from the early years of the cancer registry (since 1958), we started our cohort from January 1st 1961 and included all incident breast cancer cases from this date.

2.2.2. The Swedish patient register

This register was used to collect data on age, sex, discharge diagnosis, surgical procedures, and hospitalization dates. The percentage of the Swedish population covered by the Patient Register was 85% in 1983, and 100% from 1987 onwards [24]. The Swedish Patient Register has achieved 95% accuracy and 98% completeness regarding surgical procedures [25].

2.2.3. The Stockholm–Gotland breast cancer register (SGBC)

This register started in 1977 and includes all patients diagnosed with breast cancer in the Stockholm–Gotland region. Individual patient information regarding endocrine therapy, chemotherapy,

radiotherapy and surgery have been recorded. The treatment data are based on the treatment recommendation from the MDT (multidisciplinary team) conference for each patient. The register also holds information on tumor stage, hormone receptor status, histological subtypes, proliferation, and differentiation grade.

2.3. Identification and follow-up of colorectal cancer

The cohort started from the first diagnosis of breast cancer and continued until a diagnosis of colorectal cancer, death, emigration, or end of follow-up (December 31st, 2010), whichever came first. The ICD-7 codes we used to identify the colorectal cancer cases by histological subtypes and anatomical location included: the proximal colon (ICD-7 codes 1530, 1531 and 1536, including the cecum, ascending colon, transverse colon, hepatic flexure, the splenic flexure and appendix); the distal colon (ICD-7 codes 1532 and 1533, including the descending and sigmoid colon); and the rectum (ICD-7 code 1540, including the rectum and rectosigmoid junction). The histological type was ascertained from code 096 using the HO/HS/CANC/24.1.

2.4. Statistical analysis

Age-, sex- and calendar-specific incidence rates of colorectal cancer, as well as the subtypes, were derived from the Swedish Cancer Register and used to calculate the expected number of colorectal cancer cases. Standardized incidence ratios (SIRs) were estimated by dividing the observed number of colorectal cancer cases with the expected number of cases. SIRs for overall risk and colorectal cancer subtypes were calculated by age (15–39, 40–49, 50–59, ≥60 years), time since breast cancer diagnosis (1–4, 5–9, ≥10 years), and calendar period (1961–1985, 1986–1995, 1995–2010).

The influence of breast cancer treatment on the risk of colorectal cancer was estimated using Cox regression models estimating hazard ratios (HRs) and 95% confidence intervals (95% CIs). Breast cancer treatment was categorized into: (1) no treatment; (2) only endocrine therapy; (3) only chemotherapy; (4) only radiotherapy; or (5) other therapies combined. The endocrine therapy included tamoxifen and/or aromatase inhibitors. The former was introduced in the 1970s and the latter in the 1990s. The chemotherapy regimens consisted of CMF (cyclophosphamide–methotrexate–fluorouracil) in the 1980s followed by the introduction of FEC (5-fluorouracil–epidoxorubicin–cyclophosphamide) in the 1990s. Other substances – such as taxanes, epirubicin, herceptin and HER2 (human epidermal growth factor receptor 2) – were introduced later on. The fifth group covered endocrine-, chemo- or radiotherapy. We also analyzed the treatment data based on: (1) no treatment; or (2) any treatment; or (1) no treatment; (2) radiotherapy; (3) any medical treatment. The analyses were further stratified by age at breast cancer diagnosis under pre- or postmenopausal status (data not shown). Covariates age group (<50, 50–60, >60), tumor stage (T0–T4), side of breast (right, left, other or unknown), hormone receptor status (estrogen-receptor- or progesterone-receptor-positive, both negative, or missing), were also included in our model. The proportional hazards assumption was tested on the basis of Schoenfeld residuals after fitting a Cox regression model. None of the variables violated the assumption. A two-sided test with a significance level (α) of 0.05 was chosen. All analyses were performed using SAS 9.3 for windows (SAS Institute Inc., Cary, NC, USA).

2.5. Sensitivity analyses

During sensitivity analyses we excluded the first 2 years of follow-up in order to decrease the potential bias of the preclinical

Table 1
Basic characteristics of colorectal cancer in the breast cancer patients.

Variables		Value
1	Number of cohort members (breast cancer cases)	179,733
2	Total person-years of follow-up	1,740,482
3	Average age at entry, years	60.54 ± 12.69
4	Average follow-up, years	9.68
5	Total number of colorectal adenocarcinoma (incidence)	2571 (147.72 per 10,000 person year)
6	Adenocarcinoma in the proximal colon (incidence)	1008 (57.91 per 10,000 person year)
7	Adenocarcinoma in the distal colon (incidence)	590 (33.90 per 10,000 person year)
8	Adenocarcinoma in the rectum (incidence)	808 (10.92 per 10,000 person year)
9	Adenocarcinoma in the unspecified colon (incidence)	190 (46.42 per 10,000 person year)

stage of colorectal cancer. We also separately analyzed cohort participants whose age at recruitment was ≤ 60 years of age (data not shown).

3. Results

3.1. Basic characteristics of the studied cohorts

A total of 179,733 breast cancer cases in women were identified in the TBC cohort. The mean follow-up was 9.7 years, which yielded 1,740,482 person years. In all, 2571 colorectal adenocarcinomas, 1008 proximal colon adenocarcinomas, 590 distal colon adenocarcinomas and 808 rectal adenocarcinomas were identified (Table 1). The average age (mean \pm standard deviation) at diagnosis of breast cancer was 60.5 ± 12.7 and the average age at diagnosis of colorectal cancer after breast cancer was 74.1 ± 9.5 .

In the SGBC cohort 20,171 breast cancer cases in women were registered and, after an average of 11.2 years of follow-up, 299 colorectal adenocarcinomas were identified (116 proximal colon adenocarcinomas, 88 distal adenocarcinomas, 85 rectal

adenocarcinomas and 10 colorectal adenocarcinomas with unspecified locations). The average age at diagnosis of breast cancer was 56.8 ± 10.7 and the average age at diagnosis of colorectal cancer after breast cancer was 71.5 ± 8.9 .

3.2. Risk of colorectal cancer after a diagnosis of breast cancer

Table 2 shows SIRs for colorectal adenocarcinoma and its subtypes in the TBC cohort compared with the general population. An overall increased risk of colorectal adenocarcinoma was observed in the breast cancer cohort compared with the general population (SIR = 1.59, 95%CI: 1.53, 1.65). Adenocarcinoma in the proximal colon showed a potentially greater SIR (1.72, 95%CI: 1.61, 1.82) than in the distal colon (1.46, 95%CI: 1.34, 1.58).

In the proximal colon, the SIR for adenocarcinoma increased with age at breast cancer diagnosis (P -value for trend = 0.03). This trend was not statistically significant in the other subsites of colorectal adenocarcinoma (Table 2). For the years of follow-up after the breast cancer diagnosis, the SIR for colorectal adenocarcinoma showed a reducing trend of SIRs in general. However, a U-

Table 2
Basic characteristics of the Stockholm–Gotland breast cancer cohort (the sub-cohort) (SGBC).

Variables	Total		Colorectal cancer		Non-colorectal cancer	
Total	20,171		299	1.5	19,872	98.5
Age	56.8 ± 10.7		61.4 ± 8.3		56.7 ± 10.7	
Hormone receptor positive						
Positive	13,159	65.2	200	66.9	12,959	65.2
Negative	2797	13.9	32	10.7	2765	13.9
Missing	4215	20.9	67	22.4	4148	20.9
Breast						
Right	9800	48.6	161	53.8	9639	48.5
Left	10,362	51.4	138	46.2	10,224	51.4
Others or unknown	9	0.0	0	0.0	9	0.0
Tumor stage						
T0	3433	17.0	70	23.4	3363	16.9
T1	8557	42.4	118	39.5	8439	42.5
T2	7191	35.7	101	33.8	7090	35.7
T3	566	2.8	2	0.7	564	2.8
T4	424	2.1	8	2.7	416	2.1
Type of malignancies						
Invasive	8046	39.9	85	28.4	7961	40.1
Only non-infiltrative	1617	8.0	8	2.7	1609	8.1
Mixed invasive and non-infiltrative	10,508	52.1	206	68.9	10,302	51.8
Treatment						
Non-treatment	3291	16.3	71	23.7	3220	16.2
Only endocrine therapy	3204	15.9	62	20.7	3142	15.8
Only chemotherapy	3003	14.9	50	16.7	2953	14.9
Only radiotherapy	875	4.3	8	2.7	867	4.4
Other therapy combined	9566	47.4	106	35.5	9460	47.6
Missing	232	1.2	2	0.7	230	1.2

Table 3
Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of colorectal adenocarcinoma in the breast cancer cohort compared with the general population, 1961–2010.

	Colorectal adenocarcinoma		Adenocarcinoma of the proximal colon		Adenocarcinoma of the distal colon		Adenocarcinoma of the rectum		Unspecified colorectal adenocarcinoma	
	Obs ^a	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
	2571	1.59(1.53,1.65)	1008	1.72(1.62,1.82)	590	1.46(1.34,1.58)	783	1.57(1.46,1.68)	190	1.55(1.33,1.78)
Age at diagnosis of breast cancer										
15–49	373	1.49(1.34,1.65)	130	1.60(1.33,1.90)	98	1.44(1.17,1.75)	117	1.41(1.17,1.69)	28	1.56(1.04,2.26)
50–59	562	1.40(1.29,1.52)	208	1.51(1.31,1.73)	131	1.24(1.04,1.47)	191	1.47(1.27,1.70)	32	1.10(0.75,1.55)
≥60	1636	1.70(1.62,1.78)	670	1.82(1.68,1.96)	361	1.57(1.41,1.74)	475	1.65(1.51,1.81)	130	1.72(1.43,2.04)
P-value for trend	0.00		0.04		0.25		0.08		0.24	
Years of follow-up ^b										
1–4 years	920	1.94(1.82,2.07)	347	2.05(1.84,2.28)	212	1.73(1.51,1.98)	288	1.98(1.76,2.22)	73	2.01(1.58,2.53)
5–9 years	618	1.32(1.22,1.43)	250	1.49(1.31,1.68)	143	1.21(1.02,1.43)	185	1.26(1.08,1.45)	40	1.12(0.80,1.52)
≥10years	1033	1.54(1.44,1.63)	411	1.64(1.49,1.81)	235	1.44(1.26,1.63)	310	1.49(1.33,1.67)	77	1.52(1.20,1.90)
P-value for trend	0.00		0.00		0.06		0.00		0.11	
Calendar year										
1961–1985	1243	1.59(1.50,1.68)	478	1.74(1.59,1.91)	271	1.36(1.21,1.54)	381	1.57(1.42,1.74)	113	1.68(1.39,2.02)
1985–1995	719	1.48(1.37,1.59)	268	1.51(1.33,1.70)	159	1.38(1.17,1.61)	236	1.55(1.36,1.76)	56	1.39(1.05,1.81)
1995–2010	609	1.76(1.62,1.90)	262	1.93(1.71,2.18)	160	1.78(1.52,2.08)	166	1.56(1.33,1.82)	21	1.36(0.84,2.07)
P-value for trend	0.14		0.38		0.01		0.92		0.21	

^a Obs: observed number; exp: expected number. ^bFirst two years of follow-up were excluded.

shaped trend was observed which showed a decreasing trend until 9 years, but a potential increase after 10 years or more (Table 2). During the different calendar periods (1961–1985, 1986–1995, 1995–2010) the SIRs showed slight changes in the total large bowel except in the distal colon. An increasing trend of SIRs was observed for adenocarcinoma in the distal colon (P -value for trend = 0.01).

3.3. Influence of breast cancer treatments upon colorectal cancer risk

We did not find any statistically significant association between the different types of breast cancer treatments and risk of colorectal cancer (Table 3). Although a small increase in risk could be observed in the proximal colon compared with the other subsites, no significant results could be fully interpreted from the available data (Table 4).

4. Discussion

We found a significant 60% increased risk of colorectal cancer in women previously diagnosed with breast cancer. Breast cancer therapy, however, did not seem to influence the risk.

The strengths of our study include the large, nationwide, population-based, retrospective cohort design. The Swedish Cancer Registry covers the whole population in Sweden and the validity of diagnosis is high [23]. In contrast to previous studies we included a large number of breast cancer and subsequent colorectal cancer cases. Furthermore, we used the Stockholm–Gotland Breast Cancer Register which included treatment information. However, some potential weaknesses also exist. For example, we did not possess any information regarding lifestyle factors such as diet or body mass index etc. that might be potential confounding or shared etiological factors that influence the risk of both breast and colorectal cancer.

Sex hormones, especially estrogen, have been associated with a risk of colorectal cancer in quite a few studies [26,27]. The results, however, are controversial. Intriguingly, some studies have found that endogenous and exogenous estrogens play different roles [28]. Although the estrogen pathway is not the central pathway in colorectal cancer, it may play an important role in the initiation and progression of this malignancy [29]. More interestingly, sex hormones have been associated with colorectal cancer subtypes

by anatomical locations. For example, female predominance of cancer in the proximal colon and male predominance of cancer in the distal colon indicate that estrogen may play a role. The reason for this difference is unknown. Over the past two decades, hormone replacement therapy (HRT) in multiple prospective and retrospective cohorts has supported a protective role in the development and prognosis of colon cancer. However, the use of HRT has decreased dramatically during the last two decades because of the increased risk of breast cancer. Several epidemiological studies using data from large prospective cohorts have demonstrated that endogenous sex hormones are associated with an increased risk of colorectal cancer. It is well known that estrogen levels are elevated in breast cancer patients, which may contribute to the increased risk of colorectal cancer in this population. Interestingly, our results showed that the SIRs of colorectal adenocarcinoma changed in different age groups compared with the general population. Specifically, the SIRs showed a drop in the 50–59 age group but increased again after the age of 60. It has been reported that endogenous estrogen levels subsequently decrease after menopause for a short period, while exogenous hormones may take effect a certain time after menopause [28].

Although previous case–control studies have shown that parity, a proxy of life-long endogenous exposure to sex hormones, is associated with a decreased risk of colorectal cancer, recent cohort studies do not support this association [30]. Further analysis of the Women's Health Initiative Study data suggests that endogenous circulating estrogen concentrations in postmenopausal women increase the risk of colorectal cancer, even after adjustment for known colorectal cancer risk factors such as circulating insulin concentrations and waist circumference [31]. This has also been demonstrated in the New York University Women's Health Study, which showed a 60% increased risk of colorectal cancer in women with the highest quartile of circulating estrogen levels compared with those in the lowest quartile [32]. A lifetime exposure to high endogenous estrogen levels may lead to a greater incidence of colorectal cancer, as seen in the previous study on nuns from 1969 [33], whereas in a patient taking exogenous HRT the colon is exposed to a short, concentrated estrogenic 'dose' that may be protective.

In breast cancer patients, approximately 80% have a receptor-positive tumor resulting in a 5-year treatment with anti-hormonal

Table 4

Hazard ratios and 95% CIs of breast cancer treatment relative to the risk of colorectal adenocarcinoma.

Category	Total		Proximal colon		Distal colon		Rectum	
	Number (%)	HR (95% CI) ^a	Number (%)	HR (95% CI) ^a	Number (%)	HR (95% CI) ^a	Number (%)	HR (95% CI) ^a
Non-treatment	71(23.91)	Reference	26(22.41)	Reference	21(24.14)	Reference	21(25.00)	Reference
Only endocrine therapy	62(20.88)	0.92(0.64,1.30)	25(21.55)	1.08(0.61,1.90)	17(19.54)	0.77(0.39,1.51)	17(20.24)	0.80(0.41,1.55)
Only chemotherapy	8(2.69)	1.02(0.48,2.14)	4(3.45)	1.64(0.56,4.81)	15(17.24)	1.06(0.31,3.64)	13(15.48)	0.41(0.05,3.08)
Only radiotherapy	50(16.84)	0.99(0.68,1.42)	19(16.38)	1.08(0.60,1.97)	3(3.45)	0.88(0.45,1.73)	1(1.19)	0.88(0.44,1.76)
Other therapy combined	106 (35.69)	0.86(0.61, 1.21)	42(36.21)	1.16(0.67,2.00)	31(35.63)	0.57(0.29,1.11)	32(38.10)	0.82(0.43,1.54)
Non-treatment	71(23.91)	Reference	26(22.41)	Reference	21(24.14)	Reference	21(25.00)	Reference
Any treatment	226(76.09)	0.92(0.69,1.23)	90(77.59)	1.12(0.71,1.79)	66(75.86)	0.75(0.43,1.29)	63(75.00)	0.81(0.47,1.38)
Non-treatment	71(23.91)	Reference	26(22.41)	Reference	21(24.14)	Reference	21(25.00)	Reference
Radiotherapy	150(50.51)	0.93(0.69,1.27)	56(48.28)	1.09(0.66,1.80)	46(52.87)	0.75(0.41,1.34)	44(52.38)	0.88(0.50,1.56)
Any medical treatment	76(25.59)	0.91(0.65,1.26)	34(29.31)	1.18(0.70,1.98)	20(22.99)	0.75(0.40,1.42)	19(22.62)	0.71(0.37,1.34)

^a HR (95% CI): Hazard ratio and 95% confidence interval.

therapy (e.g., tamoxifen, aromatase inhibitors). This treatment may lower the level of estrogen by blocking the estrogen receptor or inhibiting the conversion of androgens into estrogens. However, we did not find an association between anti-hormonal therapy and any other treatments influencing the risk of colorectal cancer. Further analysis in pre- or postmenopausal women with breast cancer showed similar results (data not shown). A meta-analysis including nine related studies found that tamoxifen use was not associated with a risk of colorectal cancer, which seems consistent with the findings of our study [34]. However, some previous studies have found increased risk of secondary cancers after specific breast cancer treatments. A Dutch study, for example, found that hormone therapy was associated with an increased risk of secondary cancer, but that chemotherapy was associated with a decreased risk of secondary cancer including colon cancer [18]; other studies have not found associations between hormone therapy, chemotherapy, and risk of colon cancer after a breast cancer diagnosis [35].

A few studies have examined the risk of colorectal cancer following a diagnosis of breast cancer, but the results are conflicting. In two studies based on SEER data, a small but still significant excess of colon cancer was found, while the risk of rectum cancer was not significant [16,20]. In the aforementioned Dutch study, breast cancer patients experienced a small but significant excess risk of developing a second non-breast cancer including colon cancer [18]. Two meta-analyses, both published in 1994, have suggested an enhanced risk of colorectal cancer in breast cancer patients, which is in line with our study [26,36]. Several studies performed later on consistently found an increased risk of colon cancer and rectal cancer. For example, in a population-based longitudinal study conducted in the Netherlands [15] Soerjomataram et al. found an increased risk of colon cancer (SIR = 1.5, 95%CI: 1.1,1.8) and rectal cancer (SIR = 1.3, 95%CI: 1.0,2.0) after diagnosis of breast cancer. The SIRs were even higher in premenopausal women (point estimates of SIR were 1.8 and 2.0, but 95%CIs were not reported). In the European Prospective Investigation into Cancer and Nutrition [19], Ricceri et al. found an increased risk of colorectal cancer (SIR = 1.71, 95%CI 1.43, 2.00) after diagnosis of breast cancer. In a nested case-control study using SEER data, Kmet et al. [37] observed a twofold increase in the risk of colon cancer among breast cancer patients who had either a family history of breast cancer or a high body mass index. The different results among different studies might be due to changes in criteria for cancer diagnosis, changes in the treatment of breast cancer, and the diversity of study designs. The increased risk of colorectal cancer could be partially interpreted by the potential role of endogenous sex hormones, while another explanation for this association might be that the body's immune system is

vulnerable, or that a predisposition to genetic factors increases the risk of both breast and colorectal malignancies. If a patient is vulnerable to the development of a first cancer they may be more susceptible to the development of a second. Furthermore, shared etiological lifestyle factors, increased medical surveillance, and late adverse health effects from therapy etc. might also play contributing roles.

Collectively, in this study the risk of colorectal cancer was observed to increase in breast cancer cases. Different treatments may not alter this risk significantly. Surveillance of colorectal cancer in breast cancer patients might be clinically vigilant, although further studies with a large sample size are warranted to verify the current results.

Conflict of interest

None declared.

Authors contributions

Yunxia Lu and Anna Martling: conception and design; Yunxia Lu, Josefin Segelman: data collection and data analysis; all: results reporting and interpretation of data; Yunxia Lu: Manuscript drafting; all: contribution to critical comments and revisions; all: final approval of the version to be published.

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