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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%CIs) 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%CIs 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.

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, $\geq$60 years), time since breast cancer diagnosis (1–4, 5–9, $\geq$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