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EPIDEMIOLOGY

Incidence of other cancer diagnoses in women with breast cancer: a retrospective cohort study with 42,248 women

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Abstract

Purpose The aim of the present study was to determine whether women diagnosed with breast cancer (BC) have an increased incidence of other cancers, e.g., gastric cancer, lung cancer, skin cancer, and so on, compared to healthy women without a breast cancer diagnosis.

Methods This retrospective cohort study was based on data from the Disease Analyzer database (IQVIA) and included adult women with an initial diagnosis of BC documented in one of 1,274 general practices in Germany between January 2000 and December 2018. Women with BC were matched to women without cancer by age, index year, yearly consultation frequency, and co-diagnoses. Univariate Cox regression models were used to study the association between BC and the incidence of other cancer diagnoses.

Results 21,124 women with BC and 21,124 women (mean age: 63 years) without cancer were included. Within 10 years of the index date, 14.3% of women with BC and 10.0% of women without cancer were diagnosed with cancer ($p < 0.001$). BC was significantly associated with the incidence of other cancer diagnoses (HR: 1.42, $p < 0.001$). The strongest association was observed for respiratory organ cancer (HR = 1.69, $p < 0.001$), followed by female genital organ cancer (HR = 1.61, $p < 0.001$) and cancer of lymphoid and hematopoietic tissue (HR: 1.59, $p < 0.001$).

Conclusion The results of this study show that women with BC have an increased incidence of another cancer compared to women without cancer. Therefore, it is important to pay particular attention to the development of other malignancies during follow-up in patients with BC. This should be considered especially in patients with a proven genetic mutation.

Keywords Breast cancer · Retrospective cohort study · Respiratory organ cancer · Cancer of lymphoid and hematopoietic tissue

Introduction

Breast cancer (BC) is known as the most common cancer in women in all countries of the industrialized world, with more than one million women developing the disease every year [1, 2]. Data show that 10% of all women suffer from BC in their lifetime. In 2018, the Robert Koch Institute recorded about 70,000 BC cases in Germany [3].

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In recent decades, the relationship between BC and other cancers has garnered considerable interest. This association may be due to genetic factors. Genetic predisposition and gene mutations are major risk factors for many cancers and play an important role in the association between BC and ovarian cancer, for example [4]. The well-known BRCA1 (Breast and Ovarian Cancer Susceptibility Gene) and BRCA2 genes show an association between BC and ovarian cancer, also called hereditary breast and ovarian cancer syndrome (HBOC) [5]. The two BRCA genes were first discovered in 1994 (BRCA1) and 1995 (BRCA2) [6]. BRCA1 and BRCA2 mutations lead to an increased risk of BC, ovarian cancer (including tubal and primary peritoneal carcinomas), prostate cancer in men, pancreatic cancer, and melanoma.

This shows that women affected by these genetic mutations also have an increased risk of other cancers [7, 8]. In

terms of familial burden, BC is often associated with other cancers, such as Li-Fraumeni syndrome, which is linked with a mutation of the pt53 gene. An increased incidence risk of lung cancer, gastric cancer, colorectal cancer, ovarian cancer, and lymphoma has also been observed in affected families [9]. Women with Cowden syndrome, a genetic hamartoma tumor syndrome, have an increased risk of benign and malignant tumors in various organs such as the breast, uterus (endometrium), skin, and colon [10].

Yet, there is a lack of large-scale studies on the association between breast and several other cancer diagnoses. The aim of the present study is to determine whether women diagnosed with BC have an increased incidence of other cancers, e.g., gastric cancer, lung cancer, skin cancer, and so on, compared to healthy women without a BC diagnosis.

Methods

Database

This study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists [11]. The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to the Anatomical Therapeutic Chemical [ATC] classification system), and the quality of reported data are monitored by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany [11]. For Example, Rathmann et al. demonstrated good agreement between the outpatient DA database with German reference data with respect to the incidence or prevalence of cancer diagnoses [11]. Finally, this database has already been used in previous studies focusing on cancer [12, 13].

Study population

This retrospective cohort study included adult women (≥ 18 years) with an initial diagnosis of BC (ICD-10: C50) documented in one of 1,274 general practices in Germany between January 2000 and December 2018 (index date; Fig. 1). One further inclusion criterion was an observation time of at least 12 months prior to the index date to enable the estimation of the incidence. Patients with other cancer diagnoses (ICD-10: C00–C97 excl. C50) prior to the index date were excluded.

BC patients were matched to non-cancer patients by age, index year, yearly consultation frequency, and diagnoses documented within one year prior to the index date including diabetes (ICD-10: E10–E14), obesity (ICD-10: E66), thyroid gland disorders (ICD-10: E00–E07), liver diseases (ICD-10: B18, K70–K77), diseases of esophagus, stomach and duodenum (ICD-10: K20–K31), chronic obstructive lung disease (COPD, ICD-10: J44), and benign, in situ, or uncertain neoplasms (ICD-10: D00–D48). These comorbidities were used because they can be associated with cancer. As BC patients have much higher consultation frequencies, and a higher consultation frequency can increase the probability of the documentation of other diagnoses, we included consultation frequency per year in the matching process.

For the women with no cancer diagnoses, the index date was that of a randomly selected visit between January 2000 and December 2018 (Fig. 1).

Study outcomes and covariates

The main outcome of the study was the overall incidence of cancer (ICD-10: C00–C97) excluding BC and metastases. The incidence of cancer of the digestive organs (ICD-10: C15–C26), respiratory organs (ICD-10: C30–C39), skin (ICD-10: C43, C44), female genital organs (ICD-10: C51–C58), urinary tract (ICD-10: C64–C68), and lymphoid and hematopoietic tissue (ICD-10: C81–C96) as a function of BC were analyzed.

Statistical analyses

Differences in the sample characteristics between those with and those without BC were tested using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. Univariate Cox regression models were used to study the association between BC and the incidence of other cancer diagnoses. These models were applied separately for different cancers. To counteract the problem of multiple comparisons, p-values < 0.01 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, USA).

Results

Basic characteristics of the study sample

The present study included 21,124 women with BC and 21,124 women without cancer. The basic characteristics of the study patients are displayed in Table 1. The mean age [SD] was 63.1 years. On average, patients visited their GP

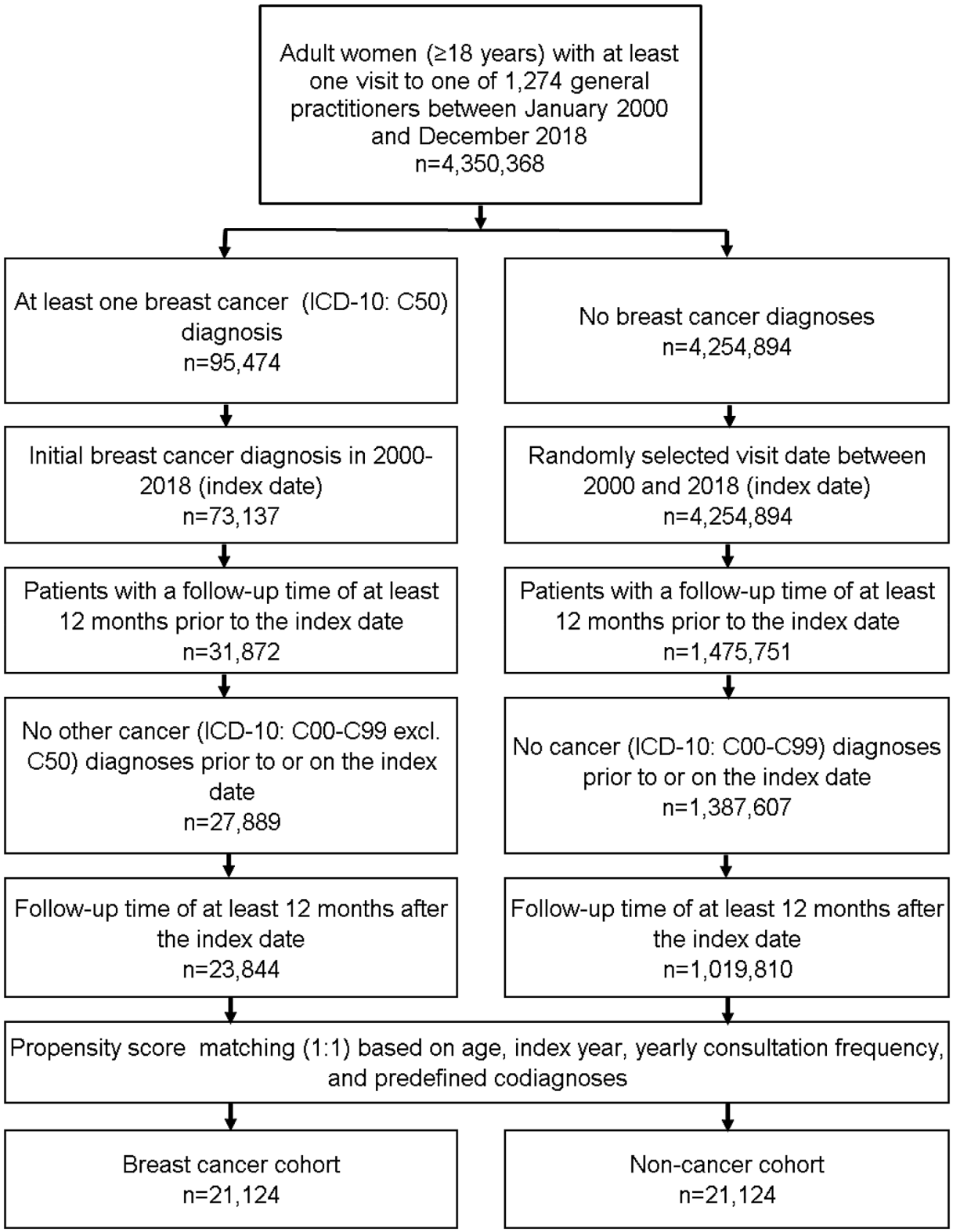

Fig. 1 Selection of study patients

Table 1 Basic characteristics of the study sample (after 1:1 propensity score matching)

Variable	Proportion affected among women with breast cancer (%) $N=21,124$	Proportion affected among women without breast cancer (%) $N=21,124$	p-value
Age (Mean, SD)	63.1 (12.8)	63.1 (13.4)	0.532
Age ≤ 50	17.7	19.0	0.133
Age 51–60	23.8	23.2	
Age 61–70	28.0	25.8	
Age > 70	30.5	32.0	
Diabetes	14.7	14.4	0.400
Obesity	9.4	9.4	0.850
Thyroid gland disorders	27.9	27.7	0.749
Liver diseases	6.1	6.4	0.146
Diseases of esophagus, stomach and duodenum	21.8	21.8	0.886
Chronic obstructive lung disease	4.3	4.5	0.299
Benign, in situ or uncertain neoplasms	7.0	6.8	0.585
Yearly consultation frequency	9.9 (8.0)	9.8 (8.0)	0.206

Proportions of patients given in % unless otherwise indicated

SD standard deviation

9.9 times per year during the follow-up period. There were no significant differences in co-diagnoses. 4.5% of breast cancer women had a distant metastasis diagnosis (ICD-10: C78, C79) within 5 years after the index date.

Association between BC and incidence of other cancer diagnoses

Within 10 years of the index date, 14.3% of women with breast cancer and 10.0% of women without cancer were diagnosed with a cancer other than breast cancer (log-rank $p<0.001$) (Fig. 2). In the regression analyses, BC was significantly associated with the incidence of other cancer diagnoses (HR: 1.42, $p<0.001$). The strongest association was observed for respiratory organ cancer (HR = 1.69, $p<0.001$), followed by female genital organ cancer (HR = 1.61, $p<0.001$) and cancer of lymphoid and hematopoietic tissue (HR: 1.59, $p<0.001$). No significant associations were observed for digestive organ and urinary tract cancer (Fig. 3).

Interestedly, the proportion of women with another cancer diagnosis was much higher in women with metastases than in women without metastases (23.0% vs. 8.9%). Nevertheless, most women with another cancer did not have a diagnosis of metastases.

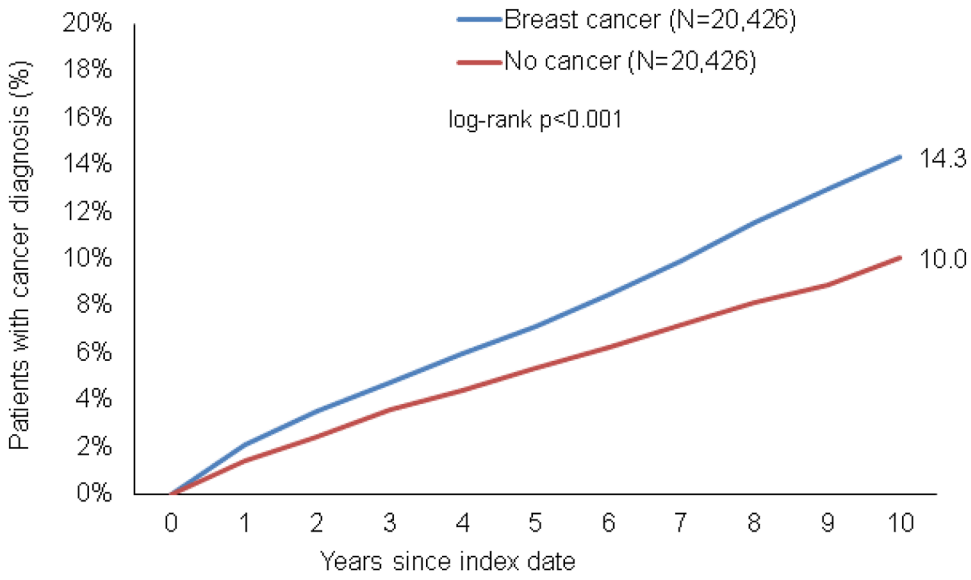

Fig. 2 Kaplan–Meier curves for time to non-breast cancer diagnosis in women with and without breast cancer

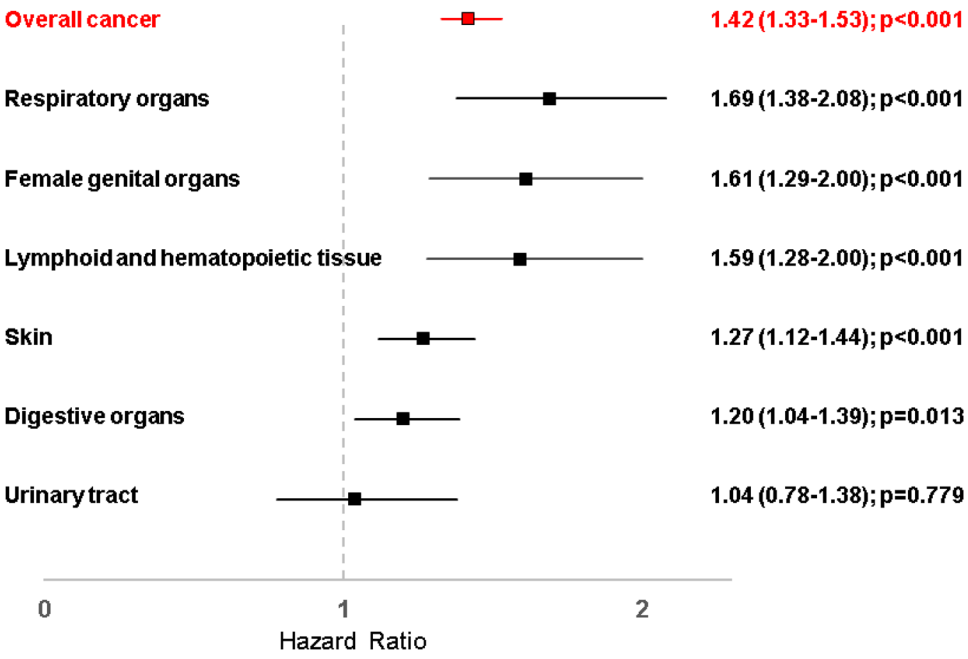

Fig. 3 Association between breast cancer and the incidence of other cancer diagnoses in women followed in general practices in Germany (Cox regression models)

Discussion

In this study, an association was observed between BC and the incidence of other cancer diagnoses. The strongest association was observed for cancer of the respiratory tract, followed by cancer of the female reproductive organs and cancer of the lymphoid and hematologic tissues.

Radiotherapy is an essential component in breast-conserving therapy in BC patients. It is strongly recommended that radiation therapy should be administered systematically after BC surgery, regardless of the extent of the disease, because it reduces local recurrence rate and thus BC-specific mortality [14, 15]. Less is known about whether radiotherapy after BC surgery leads to a higher risk of developing a second malignancy. Prochazka et al. reported a significantly increased relative risk (RR) of subsequent ipsilateral lung cancer within 10 years of radiotherapy in women with BC [16]. Lorigan et al. showed that treatment factors (i.e., type of surgery, radiotherapy technique, and adjuvant chemotherapy) and patient factors (i.e., age and smoking) have an effect on the risk of developing subsequent lung cancer. Evidence suggests that older radiotherapy techniques were associated with a substantially increased risk of developing lung cancer in the ipsilateral lung, but there is no clear evidence of increased risk with modern techniques [17].

This study also showed a strong association between BC and cancer of the female reproductive organs. Sufficient data are now available to explain the association between BC, ovarian cancer, and endometrial cancer based on genetic predisposition (BRCA mutation, Cowden syndrome, and Lynch syndrome). Following the sensational discovery of the two BRCA genes and their mutation in 1994 (BRCA1) and 1995 (BRCA2), a close relationship between breast cancer and ovarian cancer [18–20] and between breast cancer and a number of other cancers [21, 22] was revealed.

Casaubon et al. published an article indicating that one in eight women (12.5%) in the United States will develop BC during their lifetime and that BRCA1 and BRCA2 gene mutations are responsible for between 5 and 10% of all BC cases [23]. This may explain the finding of the present study that women with BC develop ovarian cancer more frequently than the collective of women without cancer diagnosis. In contrast to the previous statistic, Amin et al. showed that genetic testing in patients with a conspicuous family history of breast and ovarian cancer significantly improves therapeutic management and reduces mortality in mutation carriers [24]. In 2012, Arai et al. focused not only on genetic testing but also on surgical management in terms of risk-reducing bilateral salpingo-oophorectomy (RRSO) and risk-reducing mastectomy (RRM), which contributes to a reduced incidence of ovarian cancer/BC and lowers overall mortality in BRCA1/BRCA2 mutation carriers [25]. This may explain why ovarian and uterine cancer is positioned second to lung cancer in the present study.

However, ovarian and primary peritoneal cancers seem to derive histopathologically from Muller's epithelium. For this reason, Dubeau et al. suggested that primary ovarian epithelial, tubal, and primary peritoneal cancers are all Mullerian in origin and could be considered as a single disease entity [26]. Casey et al. stated that over 90% of peritoneal cancers in patients are associated with BRCA1 and BRCA2 mutations [27].

Laki et al. reported that there is a higher incidence risk of primary peritoneal cancer despite prophylactic

salpingo-oophorectomy. This peritoneal cancer often occurs many years later and it is only detected in advanced stages [28].

A possible association between Lynch syndrome and BC has long been discussed, but insufficient data are available to determine whether such an association actually exists. Roberts et al. noted that two LS genes, MSH6 and PMS2, are associated with an increased risk of BC and should be considered when ordering genetic testing for individuals with a personal and/or family history of BC [29].

There is a dearth of data describing the association between BC and gastric cancer. Kluz et al. conducted a study suggesting that the constellation of ovarian and gastric cancer predicts the presence of a germline BRCA2 mutation in the Polish population, confirming that gastric cancer is part of the spectrum of BRCA2 mutations [30]. Bermejo et al. conducted a large-scale retrospective population study in Swedish families that indicated a twofold increased incidence of gastric cancer in men with BRCA1 mutation carrier status [31].

The risk of colorectal cancer associated with BRCA1 and BRCA2 mutations remains unclear to date. In their study, Phelan et al. reported an increased risk of colorectal cancer in BRCA1 mutation carriers aged under 50, but not in women with BRCA2 mutations or in older women [32]. The above findings are consistent with the 2001 study by Thompson et al. which showed a slight but significant increase in colorectal cancer risk among family members of individuals with a BRCA1 or BRCA2 mutation [33]. Lu et al. described an increased risk of colorectal adenocarcinoma – especially in the proximal colon – in women with BC and a possible association between sex hormones and colorectal cancer [34]. Segelman et al. reported an increased risk of colorectal cancer after ovariectomy for benign indications compared to the general population [35].

Although previous studies have suggested a potential association between BC and colorectal cancer, Lai et al. found that patients with BC should not undergo CRC screening at intervals different than those used for the general population, and patients younger than 50 years with BC should be considered for CRC screening at age 45 years [36]. Schukla et al. also reported a similar prevalence of colorectal adenomas in BC survivors and a healthy collective of women [37].

There are data showing an association between BC and other cancers based not only on genetic predisposition, but also on BC subtype and age. El Saghir et al. found that young age at presentation was associated with a worse prognosis despite higher than expected positive hormone receptor status, more anthracycline-based adjuvant chemotherapy, and equivalent adjuvant tamoxifen hormone therapy [38]. Fredholm et al. observed that young women who developed BC had a higher risk of death than middle-aged women, even when diagnosed early and treated intensively [39]. Sung et al. observed the incidence risk of subsequent primary cancers in BC survivors in relation to hormone receptor status and age. After BC recurrence, the highest incidence rates were for ovarian cancer in HR-negative survivors with early onset, while the highest incidence rates for lung cancer were found in HR-negative survivors with early and late onset, and those for endometrial cancer in HR-positive survivors with late onset [40].

In 2022, Lee et al. reported that the use of tamoxifen, a standard therapy in premenopausal patients with BC, is associated with an increased risk of endometrial cancer [41]. Jeon et al. published a study addressing the same issue. Jeon et al. found that parity, the thickness of the endometrium, and the presence of abnormal vaginal bleeding, but not age, body mass index, and menopausal status, may be associated with endometrial pathology during the use of tamoxifen in women with BC [42].

This study also showed an association between women with BC and cancer of the lymphoid and hematologic tissues compared to a healthy collective. There are few studies describing the association between BC and cancer of the lymphoid and hematologic tissues. Kaplan et al. published a study in 2011 showing an increased risk of myelodysplastic syndrome (MDS) and acute myelodysplastic leukemia (AML) in women treated with radiation and chemotherapy compared with available population incidence data [43].

There are also few studies investigating the relationship between BC and skin cancer. Goggins et al. showed in their study that carriers of mutations in the BC predisposition gene BRCA2 have an increased risk of melanoma, while carriers of mutations in the melanoma susceptibility gene CDKN2A have a higher risk of BC than previously expected [44]. Ginsburg et al. reported that BRCA2 mutation carriers have an increased risk of skin cancer, especially basal cell carcinoma, compared to BRCA1 carriers [45]. Ho et al. described a bidirectional association between BC and malignant melanoma [46]. In their 2020 study, Arunan et al. showed that the incidence rate (SIR) of primary cutaneous melanoma after BC was higher than the incidence rate (SIR) of BC after cutaneous melanoma [47].

The three major strengths of this study are the number of women and general practices available for analysis, the duration of follow-up, and the use of real-world data. However, the present findings should be interpreted in light of several limitations. First, BC and other cancer diagnoses relied solely on ICD codes used in general physicians' practices, and no information was available as to whether these cancers were initially diagnosed by gynecologists or in hospitals. Second, no data from gynecologists' or other specialist practices and hospitals were available. Third, no information was available on TNM stage, tumor stage, hormone receptor status, chemotherapy, and radiotherapy. Fourth, there was a

lack of data on the socioeconomic and lifestyle-related risk factors of patients. Fifth, it cannot be ruled out that many of the new cancer diagnoses were breast cancer metastases, which, however, were not coded as metastases.

Conclusions

The results of this study show that women with BC have an increased incidence of another cancer compared to women without cancer. Knowing their risk of developing a new primary cancer is important not only in terms of the potential side effects of their cancer treatment, but also in terms of the possibility of a common etiology with other cancers. Therefore, it is important to pay particular attention to the development of other malignancies during follow-up in women with BC. This should be considered especially in patients with a proven genetic mutation.

Author contributions All authors contributed to the study conception and design. Analyses were performed by IN and KK. The first draft of the manuscript was written by IN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets analyzed during the current study are not publicly available due to data protection rules but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have not disclosed any competing interests.

Ethical approval The database used includes only anonymized data in compliance with the regulations of the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no Institutional Review Board approval was required for the use of this database or the completion of this study.

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