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Elevated risks of subsequent endometrial cancer development among breast cancer survivors with different hormone receptor status: a SEER analysis

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Abstract

Estrogen receptor (ER)-positive breast cancer patients treated with tamoxifen are known to have an elevated risk of subsequent endometrial cancer. However, it is unclear if ER-negative patients also have a higher risk of endometrial cancer. This population-based study aims to evaluate whether breast cancer patients with distinctive ER and PR status possess differential risks in developing delayed endometrial malignancy. Data were obtained from the Surveillance,

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Epidemiology, and End Results program (1992–2009). Standardized incidence ratio (SIR) was calculated as the observed cases of endometrial cancers among breast cancer survivors compared with the expected cases in the general population. Data were stratified by latency periods, race, age, and calendar year of breast cancer diagnosis. We identified 2044 patients who developed a second primary endometrial cancer among 289,933 breast cancer survivors. The overall SIRs for subsequent endometrial cancers were increased in all of the four subtypes (ER+PR+, ER+PR−, ER −PR+, and ER−PR−) of breast cancer. SIR was increased for all latency periods except for the initial 6–11 months after breast cancer diagnosis. Stratifying by age of diagnosis, elevated SIRs in all ER/PR groups were statistically significant among patients diagnosed with breast cancer after the age of 40. Demographically, non-Hispanic whites had increased SIRs in all subtypes of breast cancer, while Hispanic whites had no statistically elevated SIRs. Here we showed that patients with invasive breast cancer have a higher risk of developing subsequent endometrial cancer regardless of ER or PR status. The increased risk among hormone receptor-negative breast cancer survivors raises concerns whether common etiological factors among these breast cancer subtypes increase the susceptibility to develop endometrial cancer. Lower threshold for routine endometrial cancer surveillance may be warranted.

Keywords

Subsequent endometrial cancer; Increased risk; First primary breast cancer; ER/PR status

Introduction

Recent advances in early screening, detection, and treatment of breast cancer have led to significant improvement in patient outcomes. While the mortality rate increased 0.4 % per year between 1975 and 1990, it has steadily decreased 1.8–3.2 % annually since 1993 [1]. Because breast cancer survivors are living longer, they have a higher risk of developing a second primary malignancy in their life time. A prior study showed that approximately 10 % of breast cancer patients develop a second cancer within 10 years after their initial diagnosis [2]. Tamoxifen, a partial agonist of estrogen receptor (ER) in the endometrium, is widely used in ER-positive breast cancers to prevent its recurrence. However, it is well documented that these patients have a significantly higher risk of developing a subsequent endometrial cancer (the most common gynecologic malignancy) among breast cancer survivors [3–6]. Nevertheless, whether such an elevated risk of developing subsequent endometrial cancers can be found in ER- and progesterone receptor (PR)-negative breast cancer patients, who most likely did not receive tamoxifen therapy, is unclear. Additionally, no study has evaluated the impact of differential ER and PR statuses in the initial breast cancer, upon the risk of a second endometrial cancer. Since breast cancers of distinctive ER and PR status are likely driven by unique molecular processes that mediate oncologic transformation, it is interesting to know whether breast cancer patients with different molecular subtypes would have different risks of developing additional gynecologic malignancies. To answer this question, we analyzed the risk of subsequent endometrial cancers among breast cancer survivors by the ER and PR status of primary breast cancer, using data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program.

Risk stratification for endometrial cancer in breast cancer survivors can help achieve earlier detection and improved survivals, as well as better understanding of the underlying oncogenesis. Therefore, this population-based study may be helpful to improve the endometrial cancer surveillance protocol.

Materials and methods

Study participants and follow-up

We analyzed invasive breast cancer patients diagnosed between January 1, 1992 and December 31, 2009 who were reported in the SEER 13 Registries. The National Cancer Institute's SEER program collects information on cancer incidence, survival, as well as patient demographics from several geographically defined regions in the United States. We selected women between the ages of 20 and 84 who were diagnosed with invasive breast cancer and survived at least 6 months. Patients older than 84 years of age were excluded to avoid confounding influence of under-reported second malignancies, competing medical comorbidities, and limited life expectancies [7]. We also excluded cases derived only from death certificates or autopsy. Endometrial cancers diagnosed within 6 months of breast cancer diagnosis were excluded as these were likely to be pre-existing or synchronous cancers. Follow-up continued until date of diagnosis of any second cancer, death from any cause, date of last known vital status, attained age 85, or end of study (December 31, 2009).

There were 342,942 women with invasive breast cancers who survived ≥6 months who were diagnosed between 1992 and 2009. Our analysis of late endometrial cancer after breast cancer included 188,635 women with ER+PR+ breast cancer, 35,364 women with ER+PR −breast cancer, 6929 women with ER−PR+ breast cancer, and 59,005 women with ER−PR− breast cancer. There were an additional 53,009 women with unknown ER and/or PR status who were excluded from our analysis.

The Johns Hopkins Medicine Institutional Review Board reviewed this study and declared it exempt because of a lack of protected health information contained in the databases used. And no consent was needed in this study.

Statistical analysis

To compare the relative risk with the general population, we used SEER*Stat Multiple primary-standardized incidence ratios (SIRs) program (version 8.1.5) to calculate SIRs by dividing the observed numbers of subsequent endometrial cancer by the expected numbers of subsequent endometrial cancer based on the rates for general population, along with their 95 % confidence interval (95 % CI). SIRs were stratified by age at diagnosis of the first primary malignancy (20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years), latency periods (6–11, 12–59, 60–119, and 120+ months), race of patients (non-Hispanic white, Hispanic white, Black, and Others), and calendar year of breast cancer diagnosis (1992–1994, 1995–1999, 2000–2004, and 2005–2009). All *P* values were two-sided and considered statistically significant when $P < 0.05$.

Results

We identified 2044 invasive breast cancer patients who developed a second primary endometrial cancer from a total of 289,933 patients with known ER/PR status. Demographics of overall observational population are shown in Table 1. Among the 2044 patients who developed a second primary endometrial cancer, there were 1427 ER+PR− patients, 244 ER+PR+, 63 ER−PR+, and 310 ER−PR− patients.

The SIRs for second primary endometrial cancers were significantly increased in all of the four subtypes of breast cancer: ER+PR+ breast cancer (SIR 1.59; 95 % CI, 1.51–1.67), ER +PR− breast cancer (SIR 1.45; 95 % CI, 1.27–1.64), ER−PR+ breast cancer (SIR 1.84; 95 % CI, 1.41–2.35), and ER−PR− breast cancer (SIR 1.37; 95 % CI, 1.22–1.53). The elevated SIRs after these four breast cancer subtypes were observed in all latency periods except the first 6–11 months after breast cancer diagnosis (Table 2). We then stratified SIRs by age at diagnosis of the first primary breast cancer with different ER and PR statuses. The SIRs for ER+PR+ or ER−PR− patients were increased with statistical significance in patient who were diagnosed for breast cancer after the age 40, while the SIRs for ER+PR− breast cancer increased in the 40–49 age group and ≥60 age group. The SIRs for ER−PR+ breast cancer were elevated only for patients diagnosed between ages 40–49 and ≥70 (Table 2). In addition to analyze the increased risk of developing endometrial cancer among breast cancer survivors stratified by latency periods and age of initial breast cancer diagnosis, we also calculated SIRs for different racial groups as well. Non-Hispanic whites showed increased SIRs after all these four subtypes of breast cancer, while the SIRs of Hispanic whites were not statistically elevated after any subtypes of breast cancer; Blacks appeared to have increased SIRs in both ER+PR+ and ER−PR− breast cancer survivors. We observed high SIRs for other populations (Asian or American Indian or other) in ER+ breast cancer patients (Table 2). The largest SIR was observed among Asian or American Indian (or other race) women diagnosed with ER+PR− breast cancer (SIR 3.24; 95 % CI, 2.19–4.63). Finally, we stratified SIRs by calendar year of breast cancer diagnosis. Subsequent SIRs are shown in Table 2 as well.

Discussion

Hormone receptors such as ER play an important role in normal breast and endometrial tissue developments. Genetic alterations, including polymorphism in the ER gene locus, have been shown to increase the risk of ER-positive breast cancer development [8]. Progesterone, on the other hand, is known to exhibit protective effects within the endometrium. PR expression in breast cancers is shown to be a putative marker of functional ER signal pathway [9]. Several studies have demonstrated that ER+PR+, ER+PR−, and ER −PR+ breast tumors showed distinct clinicopathological characteristics and outcomes [10–14]. In the current study, we found that the overall risk of developing a second primary endometrial cancer is significantly increased in breast cancer patients regardless of their expression of ER and PR. This increased risk was also noted in both premenopausal and postmenopausal patients. Interestingly, patients with both ER+PR+ and ER−PR− breast cancers that were diagnosed after the age of 40 had increased risk for developing a endometrial cancer, whereas the increased incidences of endometrial cancer appear to be

bimodal for ER+PR− and ER−PR+ breast cancer survivors. The results raise important concerns regarding the pathogenesis of cancers in young and elderly patients. As in the case of breast cancers, even when exhibit similar histological features, they appear to behave differently between younger and older patients in terms of aggressiveness. This observation is likely driven by multifactorial process including several molecular and biological distinctions. But how these age-related differences apply to the development of other hormone sensitive tumors remains uncertain. Clear risk stratification for subsequent endometrial cancer development among breast cancer survivors with different ER/PR statuses could achieve earlier detection and better understanding of the underlying pathogenesis.

Our results identified a demographical preference in the risk of subsequent endometrial cancer development among breast cancer survivors. Non-Hispanic whites showed increased risks in all four subtypes of breast cancer survivors, while Hispanic whites were unlikely to develop subsequent endometrial cancer after breast cancer. Lower overall incidence of endometrial cancer among Hispanic whites (14.04; 95 % CI, 13.39–14.72) compared with non-Hispanic whites (23.43; 95 % CI, 23.06–23.81) may be a contributing factor [15]. The largest SIR was observed among Asian or American Indian women diagnosed with ER+PR− breast cancer; therefore, these people may need to have a lower threshold for routine surveillance of endometrial cancer.

Our findings support the previous studies that reported an elevated risk of endometrial cancer after ER-positive breast cancer [4–6]. These studies found an increased risk of subsequent endometrial cancer in ER-positive breast cancer patients with tamoxifen therapy, but no study has reported the risk after ER-negative breast cancer. Indeed, we found that ER −PR− breast cancer who most likely did not receive tamoxifen therapy also had a significantly increased risk of endometrial cancer, especially during the years of 2005–2009 of breast cancer diagnosis, in which period the ER- or PR-positive survivors who have a much higher prevalence of tamoxifen treatment did not show any statistically elevated risks of subsequent endometrial cancer. These observations suggest that tamoxifen use may not be the only reason for the elevated risk of second primary endometrial cancer after breast cancer. A recent study has found an increased risk of a second endometrial cancer in breast cancer survivors who did not receive tamoxifen therapy partly confirmed our results, although no ER/PR status of breast cancer was analyzed [16]. People may doubt why ER or PR positive patients who were diagnosed during 2005–2009 did not show any increased risks of endometrial cancer, but patients diagnosed before 2005 had significant elevated risk in the analysis. The largest case–control study found that patients with tamoxifen use for less than 2 years failed to show statistically increased risk for developing endometrial cancer [17]. The follow-up of our study continued until December 31, 2009, giving the fact that lots of ER/PR positive breast cancer patients diagnosed during 2005–2009, may have undergone tamoxifen treatment less than 2 years, so tamoxifen’s effect on subsequent endometrial cancer development among these patients was underestimated. Thus, the second primary endometrial cancer risk correlating with duration of tamoxifen use might be a potential reason. Underlying genetic susceptibility may contribute to a shared risk of breast and endometrial cancers. For example, BRCA1/2 gene mutations that are usually seen in triple negative breast cancer would also increase the risk of endometrial cancer, especially in the

patients who were diagnosed with breast cancer at an early age [18, 19]. In elderly patient who were previously diagnosed with ER−PR− negative breast cancer, the factors that increased their endometrial cancer risks would likely be more environmental, rather than genetic [20–24]. In addition, a population-based retrospective study conducted in the Netherlands reported chemotherapy was associated with increased risk of endometrial cancer among breast cancer survivors who were diagnosed at 50 years or older [25]. Since hormone receptor-negative breast cancer patients are more likely to undergo chemotherapy, systemic chemotherapy may lead to the elevated risk of subsequent endometrial cancer. Unfortunately, it was not possible for us to further assess the exact impact of chemotherapy on the risk due to the lack of systemic treatment information in the SEER database.

As mentioned above, we failed to find an association between endometrial and breast cancers before the age of 40. This result is consistent with an EBCTCG meta-analysis which reported a significant elevated risk of subsequent endometrial cancer among breast cancer survivors (the overall breast cancer group contained both ER-positive and ER-negative patients) after 45 years old, and no statistical difference in breast cancer patients diagnosed before 45 [26]. In this meta-analysis, tamoxifen, compared with placebo, resulted in a significantly increased risk of endometrial cancer for women ≥50 years old (2.6 versus 0.8 %; RR = 3.32), but not for women <50 years old (0.3 versus 0.3 %; RR = 1.19) [26]. Based on the current study's finding that endometrial cancer risks are increased for ER+PR+, ER +PR−, ER−PR+ breast cancers in the 40–49 age group, it is possible that the shared risk factors such as obesity, hormone replacement therapy, and reproductive factors may contribute to the elevated risk of endometrial cancer in these patients [20–24]. Additionally, several studies have reported higher incidence of chemotherapy-induced amenorrhea (CIA) in premenopausal ER-positive breast cancer patients [27–29]. The low estrogenic environment caused by chemotherapy along with tamoxifen treatment may lead to the activation and increased synthesis of endometrial estrogen and progesterone receptors, which may also contribute to increased risk of endometrial cancer [30, 31].

For the first time, we show that the risk of a subsequent endometrial cancer is increased after breast cancer, regardless of their ER and PR status, based on a large number of patients from population-based registries. Moreover, our study provides an in-depth assessment of the effects of latency period, race, age, and year of primary cancer diagnosis on the risk of subsequent endometrial cancer among breast cancer survivors. However, similar to other studies that relied on SEER database, our study also suffers from lack of detailed breast cancer treatment data (chemotherapy, hormone treatment, and ovarian suppression), information regarding lifestyle (diet, hormone replacement), genetic cancer risk factors, and important clinico-pathological characteristics (BMI, menstrual status, ER/PR status of endometrial cancer).

Conclusions

In summary, this study showed that patients with previous history of invasive breast cancer have a higher risk of developing a subsequent endometrial cancer, regardless of the ER or PR status of breast cancer. The elevated risk in patients with hormone receptor-negative breast cancer raises concerns that besides tamoxifen treatment, shared etiological factors

such as genetic susceptibility, hormone replacement therapy, and behavioral factors between these cancers may also play a role. The association between endometrial and breast cancers suggests that the endometrial cancer surveillance protocol may need to be revised to a lower threshold, even for patients with ER- and PR-negative tumors. Further studies with detailed tumor characteristics, lifestyle and genetic risk factors, as well as treatment information, are required to understand the associations and the underlying mechanisms better.

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Abbreviations

ER	Estrogen receptor
PR	Progesterone receptor
SEER	Surveillance, epidemiology, and end results
SIRs	Standardized incidence ratios
CI	Confidence interval
RR	Relative ratio
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
CIA	Chemotherapy-induced amenorrhea
BMI	Body mass index

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Table 1

Characteristics of the invasive female breast cancer survivors with known ER and PR status

Characteristic	No. of first primary breast cancers	No. of person-years
Total no.	289,933	1,875,381.77
Breast cancer subtypes		
ER+PR+	188,635	1,243,124.44
ER+PR−	35,364	223,021.27
ER−PR+	6929	54,917.03
ER−PR−	59,005	354,319.03
Race		
Non-Spanish White	211,842	1,423,751.83
Spanish white	23,676	134,274.71
Black	25,646	141,763.90
Others	28,769	175,591.33
Age at breast cancer diagnosis, years		
20–29	1715	10,701.05
30–39	17,800	119,553.67
40–49	59,625	407,358.00
50–59	74,050	488,372.47
60–69	65,679	431,327.07
70+	71,064	418,069.51
Time since breast cancer diagnosis, years		
1992–1994	39,904	449,788.47
1995–1999	77,411	724,138.22
2000–2004	86,250	522,268.16
2005–2009	86,368	179,186.92

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Table 2

Subsequent endometrial cancer among invasive female breast cancer survivors according to ER and PR status

Characteristic	Subsequent endometrial cancers in survivors of ER+PR+ breast cancer			Subsequent endometrial cancers in survivors of ER+PR− breast cancer			Subsequent endometrial cancers in survivors of ER−PR+ breast cancer			Subsequent endometrial cancers in survivors of ER−PR− breast cancer		
	O[§]	E[•]	SIR (95 % CI)	O	E	SIR (95 % CI)	O	E	SIR (95 % CI)	O	E	SIR (95 % CI)
Total no.	1427	898.54	**1.59**[*] (1.51–1.67)	244	168.47	**1.45**[*] (1.27–1.64)	63	34.27	**1.84**[*] (1.41–2.35)	310	225.94	**1.37**[*] (1.22–1.53)
Age at breast cancer diagnosis, years												
20–29	0	0.21	0 (0–17.19)	0	0.04	0 (0–86.14)	0	0.02	0 (0–165.95)	0	0.21	0 (0–17.19)
30–39	9	9.97	0.90 (0.41–1.71)	3	1.58	1.90 (0.39–5.54)	2	1.05	1.90 (0.23–6.85)	7	5.81	1.20 (0.48–2.48)
40–49	187	114.59	**1.63**[*] (1.41–1.88)	24	13.73	**1.75**[*] (1.12–2.60)	22	8.00	**2.75**[*] (1.72–4.16)	54	38.45	**1.40**[*] (1.05–1.83)
50–59	342	252.77	**1.35**[*] (1.21–1.50)	53	47.32	1.12 (0.84–1.46)	14	11.54	1.21 (0.66–2.04)	96	76.77	**1.25**[*] (1.01–1.53)
60–69	441	273.52	**1.61**[*] (1.47–1.77)	88	54.95	**1.60**[*] (1.28–1.97)	12	7.97	1.51 (0.78–2.63)	90	61.63	**1.46**[*] (1.17–1.79)
70+	448	247.48	**1.81**[*] (1.65–1.99)	76	50.85	**1.49**[*] (1.18–1.87)	48	5.69	**2.29**[*] (1.22–3.91)	63	43.05	**1.46**[*] (1.12–1.87)
Latency period, months												
6–11	70	61.17	1.14 (0.89–1.45)	16	12.26	1.30 (0.75–2.12)	3	1.76	1.71 (0.35–4.99)	18	15.95	1.13 (0.67–1.78)
12–59	616	404.36	**1.52**[*] (1.41–1.65)	98	78.33	**1.25**[*] (1.02–1.52)	21	12.44	**1.69**[*] (1.05–2.58)	127	98.73	**1.29**[*] (1.07–1.53)
60–119	508	302.14	**1.68**[*] (1.54–1.83)	100	54.79	**1.83**[*] (1.49–2.22)	24	11.95	**2.01**[*] (1.29–2.99)	103	72.98	**1.41**[*] (1.15–1.71)
120+	233	130.87	**1.78**[*] (1.56–2.02)	30	23.10	1.30 (0.88–1.85)	15	8.12	**1.85**[*] (1.41–2.35)	62	38.28	**1.62**[*] (1.24–2.08)
Race												
Non-His[#] White	1154	744.98	**1.55**[*] (1.46–1.64)	194	136.95	**1.42**[*] (1.22–1.63)	55	26.63	**2.07**[*] (1.56–2.69)	217	168.97	**1.28**[*] (1.12–1.47)
His[#] White	67	56.71	1.18 (0.92–1.50)	10	11.85	0.84 (0.40–1.55)	4	2.57	1.56(0.42–3.99)	24	18.65	1.29 (0.82–1.91)
Black	77	42.8	**1.80**[*] (1.42–2.25)	10	10.41	0.96 (0.46–1.77)	2	2.57	0.78(0.09–2.81)	48	23.56	**2.04**[*] (1.50–2.70)
Others	129	54.04	**2.39**[*] (1.99–2.84)	30	9.26	**3.24**[*] (2.19–4.63)	2	2.51	0.80 (0.10–2.88)	21	14.76	1.42 (0.88–2.17)
Calendar year of breast cancer diagnosis												
1992–1994	375	215.89	**1.74**[*] (1.57–1.92)	55	43.93	1.25 (0.94–1.63)	25	12.27	**1.96**[*] (1.27–2.90)	82	59.23	**1.38**[*] (1.10–1.72)
1995–1999	620	355.11	**1.75**[*] (1.61–1.89)	115	62.89	**1.83**[*] (1.51–2.19)	23	14.86	1.55 (0.98–2.32)	122	86.03	**1.42**[*] (1.18–1.69)
2000–2004	339	246.94	**1.37**[*] (1.23–1.53)	60	46.68	1.29 (0.98–1.65)	12	5.40	**2.22**[*] (1.15–3.88)	72	59.42	1.21 (0.95–1.53)
2005–2009	93	80.59	1.15 (0.93–1.41)	14	14.98	0.93 (0.51–1.57)	3	1.28	2.34 (0.48–6.85)	34	21.26	**1.60**[*] (1.11–2.23)

The bold values indicate the SIR (risk) for developing a second primary endometrial cancer was significantly increased

SIR standardized incidence ratios

[*] $P < 0.05$; Confidence Intervals are 95 %

[§] Observed number

[°] Expected number

[#] Hispanic