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Short communication

Secondary gastric cancer malignancies following a breast cancer diagnosis: A population-based analysis

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ABSTRACT

Objective: To quantify the population-risk of developing gastric cancer (GC) following breast cancer (BC).
Methods: GC incidence following a ductal or lobular BC were separately compared to incidence in the general United States population using SEER data.
Results: GC rates were similar to the general population for ductal BC. Women aged 35–75 with lobular BC had a significantly higher incidence of GC; women aged 40–44 had the highest risk.
Conclusion: The risk of secondary GC is high among young women diagnosed with lobular BC. More studies investigating the etiology and prevalence of familial GC syndromes at the population-level are needed.

1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women in North America and Europe [1], and the most common cancer in female cancer survivors [2]. Survivorship is a critical component of caring for curatively-treated BC patients, including screening for secondary cancers. The development of secondary malignancies are a growing concern for BC survivors [3], given the current survival for women following BC treatment [4,5]. Women with a first primary BC make up 25% of cancer survivors diagnosed with a secondary malignancies [3].

BC patients with select genetic mutations may be at risk for developing a second gastric cancer (GC), which is more often diagnosed with metastases and has dismal prognosis in low incidence countries. Hereditary diffuse gastric cancer syndrome is the prototypical familial GC syndrome (FGCS) and associated with a mutation in the CDH1 gene. HDGC predisposes up to 80% of patients to diffuse-type gastric cancer and up to 45% to lobular-type BCs. Other important genetic disorders that may increase the co-occurrence of breast and GC include Li-Fraumeni syndrome (5% develop GC), Peutz-Jeghers syndrome (2–3%), and other hereditary BC syndromes [6]. Early identification of BC patients with FGCS enables intensified screening, prophylactic surgery, and identification and counseling of relatives at risk [7].

The objective of this study was to quantify the risk of developing GC following a diagnosis of a BC at the population level.

2. Methods

The study populations were identified using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database from nine registries, covering 9.5% of the United States population. SEER data are publicly available and do not require local institutional ethics board approval.

Female BC patients diagnosed between 1973 and 2011 were included. Ductal and lobular BCs were examined separately, as ductal tumor pathology is not considered part of the FGCS. Ductal BC and lobular BC were identified using the ICD-O-3 codes C500-C506, C508-C509 and the histology codes 8500/3 and 8520/3

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respectively. Individuals under 20, diagnosed on death certificate or autopsy only, or with a previous cancer diagnosis were excluded. GC diagnoses (ICD-0-3 codes C160-C166, C168-C169) were measured. GC diagnoses were measured beginning two months from the BC diagnosis until the date of death or last follow-up [8].

GC risk was estimated using standardized incidence ratios (SIRs) with 95% confidence intervals (95%CI), defined as the ratio of observed GC cases to the number of expected GC cases [9]. SIRs were calculated and stratified into categories by 5-year age at BC diagnosis. SIRs were further stratified by latency periods from the time of index cancer diagnosis, estimating the occurrence of GC in the subsequent 2–11 months, 12–59 months, 60–119 months, and ≥120 months. Excess absolute risks (EAR) were calculated to estimate the absolute number of excess GC cases observed that may be attributable to FGCS. Statistical tests were 2-sided and p-values of less than 0.05 were considered significant. All analyses were performed using Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.1.5.

3. Results

Table 1 describes the two cohorts and reports the observed and expected number of GC cases, stratified by age at BC diagnosis. Females diagnosed with a lobular BC (SIR 1.84, 95%CI: 1.53–2.19) had an increased relative risk of developing a GC.

All women diagnosed with lobular BC before the age of 75 years old demonstrated a significantly increased relative risk of developing a GC compared to the general US population (Fig. 1). The risk of developing a GC was higher among younger women with a lobular BC diagnosis, compared to older women with lobular BC.

The largest excess risk was observed in women diagnosed between 40 and 44 years old, with almost 3 additional GC cases diagnosed per 10,000 persons per year. In this age category, this represented a 509% increased relative risk of developing a GC. The magnitude of this risk increase then declined progressively with advancing age at the time of lobular BC diagnosis (by 5-year age increments).

The results of the latency period analysis did not identify any obvious, clinically significant time periods of increased GC risk (Supplementary Tables). The increased risk appeared to begin within 60 months of index cancer diagnosis. A signal was seen as early as 12–59 months in women aged 60–64 years old, but did not reach statistical significance.

4. Discussion

This is the first large, population-based study from North America to support the findings of a potential shared genetic mutation in lobular BC and gastric cancer [10–12]. Our study identified that women with a lobular BC diagnosis have a significantly increased risk of developing a secondary GC, although the absolute numbers are small, while demonstrating no increased risk of GC for women with ductal BC. We identified an 84% increased incidence of GC after a lobular BC, compared to the general United States population. Our findings highlight the highest risk among young individuals diagnosed before age 75.

We hypothesize that excess risk in young women with lobular BC may be attributed to HDGC syndrome and other CDH1-related familial cancer syndromes. However, this study is limited by the inability to distinguish histologic types of gastric cancer. Our hypothesis is supported by our reported lack of association between ductal BC, a tumor pathology that is linked to Li-Fraumeni and Peutz-Jeghers syndromes. In addition, were the increased risk due to environmental factors or initial cancer therapy, risk should not differ between patients diagnosed with lobular versus ductal BC given their similar treatment protocols. In contrast, a recent study using SEER data reported a lower than expected incidence of BC in a cohort of GC patients [13]. These contradictory findings may be the result of the high mortality associated with a first GC primary, especially in North America where the majority of patients are diagnosed with non-curative disease.

These results provide further evidence that research into familial syndromes linking breast and GC is necessary. HDGC is typically associated with more CDH1 gene mutations of e-cadherin; however, many HDGC families are negative, suggesting alternate gene mutations or familial syndromes [14]. In addition, the global number of HDGC families is unspecified. The strong association

Table 1
Observed and expected gastric cancer diagnoses in ductal and lobular BC patients, with standardized incidence ratios (SIRs) and 95% confidence intervals (95%CI).

Index Cancer Diagnosis	Persons Observed	Person Years at Risk	Observed # GC Cases	Expected # GC Cases	Excess Risk	SIR (95% CI)
Ductal Breast						
All Ages	349,813	3,329,052	674	646	0.08	1.04 (0.97–1.13)
40–44	27,554	313,539.51	22	17.26	0.15	1.27 (0.8–1.93)
45–49	37,583	417,650.43	32	33.21	−0.03	0.96 (0.66–1.36)
50–54	40,558	430,991.44	59	48.4	0.25	1.22 (0.93–1.57)
55–59	41,655	425,828.83	71	66.13	0.11	1.07 (0.84–1.35)
60–64	41,575	413,427.26	97	87.75	0.22	1.11 (0.9–1.35)
65–69	39,133	374,022.61	112	104.53	0.2	1.07 (0.88–1.29)
70–74	34,297	295,626.43	97	103.93	−0.23	0.93 (0.76–1.14)
75–79	28,708	209,458.17	69	89.35	−0.97	0.77 (0.60–0.98)
80–84	19,479	111,776.98	68	55.34	1.13	1.23 (0.95–1.56)
85+	14,357	57,224.29	35	30.8	0.73	1.14 (0.79–1.58)
Lobular Breast						
All Ages	36,222	332,128	124	68	1.7	1.84 (1.53–2.19)
40–44	2002	23,943.29	8	1.31	2.79	6.09 (3.00–12.00)
45–49	3662	41,729.97	8	3.24	1.14	2.47 (1.00–4.86)
50–54	4038	43,631.57	12	4.66	1.68	2.58 (1.33–4.50)
55–59	4062	40,646.17	14	5.86	2	2.39 (1.31–4.01)
60–64	4440	42,740.13	18	8.34	2.26	2.16 (1.28–3.41)
65–69	4514	41,908.97	19	10.78	1.96	1.76 (1.06–2.75)
70–74	4259	35,694.87	21	11.72	2.6	1.79 (1.11–2.74)
75–79	3632	26,461.16	10	10.43	−0.16	0.96 (0.46–1.76)
80–84	2583	14,845.55	10	6.71	2.22	1.49 (0.71–2.74)
85+	2040	8053.49	2	4	−2.48	0.5 (0.06–1.81)