Studying the Association Between Breast Cancer and Renal Cell Carcinoma

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Abstract

Purpose:

There are case reports of patients with both primary breast cancer (BC) and renal cell carcinoma (RCC). We explore the association between these two malignancies using SEER population data and our institutional records.

Methods:

We studied the association between BC and RCC in the 2000-2016 Surveillance, Epidemiology and End Results (SEER) database. We then reviewed our hospital records of patients with both BC and RCC and collected information including personal and family history of cancers, genetic testing, and patient outcomes.

Results:

Of the 813,477 females diagnosed with BC in the SEER database, 1,914 later developed RCC. The risk of developing RCC was significantly increased within the first six months, 7-12 months, and 1-5 years following BC diagnosis with standardized incidence ratios (SIRs) of 5.08 (95% CI, 4.62- 5.57), 2.09 (95% CI, 1.8-2.42), and 1.15 (95% CI, 1.06-1.24), respectively. Of 56,200 females with RCC, 1,087 later developed BC. The risk of developing BC following RCC was elevated within the first six months (SIR of 1.45 [95% CI, 1.20-1.73]). For our hospital patients, 437 had both BC and RCC. 427 (97.71%) were female, and 358 (81.92%) were white, and breast cancer was diagnosed before RCC in 246 (61.5%) patients. There were 15 germline mutations in those with genetic testing.

Conclusion:

Our findings suggest that BC patients are at higher risk of developing RCC and vice versa. BC tended to precede RCC, and patients frequently had personal histories of other malignancies and a family history of cancer, particularly BC.

1. Introduction

There are several cancers that are known to be associated with one another, usually as a result of having a common risk factor. Classic examples of such risk factors include mutations in genes such as BRCA that increase the risk of breast cancers and ovarian cancers¹, and smoking as well as alcohol intake that are associated with increased risk of both lung and head-and-neck cancers². Additionally, patients who have undergone chemotherapy with certain agents are at higher risk for future cancers such as leukemia³.

There are several case reports describing patients with both primary RCC and malignant breast neoplasms⁴⁻⁹. It is estimated that in the US 281,550 women and 2,650 men will be diagnosed with BC in

2021¹⁰. Furthermore, an expected 43,600 women and 530 men will die in the US due to BC in 2021. The American Cancer Society also estimates that there will be approximately 76,080 new cases of renal cancer in the US resulting in 13,780 deaths.

Aside from a handful of case reports, studies elaborating on the phenomenon of patients with both primary breast and renal cancer are very limited. In a study by Beislan et al assessing 1,425 patients with RCC, 26 (1.8%) had a history of breast cancer as well¹¹. Another study by Demir et al with 1,129 cases of RCC had 13 patients (1.15%) with BC¹². This data prompted us to evaluate the potential association between BC and RCC. We started by conducting a population analysis using the Surveillance, Epidemiology, and End Results (SEER) database, then proceeded to review our hospital records to explore the population of patients with both breast cancer and RCC.

2. Methods

2a - SEER National Population Analysis Methods

Data source:

We obtained data from the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute, using the SEER*stat software (version 8.3.5). We used the SEER 18 registries (2017 submission) covering about 27.8% (based on the 2010 census) of the US population between 2000 and 2017^{13,14}.

Study population:

We reviewed patients diagnosed with BC between 2000 and 2016 and followed them for a later diagnosis of RCC, and then reviewed patients diagnosed with RCC in the same time frame and followed them for a later diagnosis of BC. We only included cases with histologic confirmation. In order to eliminate the possibility of an incorrect order of cancer onset, we excluded cases with RCC diagnosed less than two months from the initial BC diagnosis and vice versa.

Outcomes :

We calculated the Standardized Incidence Ratios (SIR) of RCC following BC diagnosis and the SIR of BC following RCC diagnosis. The 'Observed' value represents the number of the second BC or RCC cancer cases diagnosed after the initial BC or RCC diagnosis, while the 'Expected' value represents the number of BC or RCC cases expected to be diagnosed in a demographically similar population within the same period. The SIR represents the change in RCC risk following BC diagnosis and vice versa when compared to the general US population.

Statistical analysis:

We used the Multiple Primary SIR session of the SEER* stat software (version 8.3.5) to calculate the standardized incidence ratios (SIR) with 95% confidence intervals (CI). A significant positive increase in the risk of BC/RCC was defined as the number of observed BC/RCC cases being more than the number of expected BC/RCC cases in the general population. The patient baseline characteristics and demographics were compared, categorical variables were compared with the Mantel-Haenszel chi-square test, and continuous variables were compared with student t-test if normally distributed and expressed as means or by the analysis of variance testing and expressed as medians if not normally distributed. Statistical analyses were conducted using RStudio software (RStudio, Boston, Massachusetts) or SPSS software, version 26 (IBM SPSS Statistics, IBM, Armonk, New York) ¹⁵. A 2-sided value of $p < 0.05$ was set for statistical significance.

2b - Hospital Patient Population Analysis Methods

IRB approval was obtained via our institutional IRB review committee, and informed consent was waived as this was a retrospective study. We used various ICD diagnoses for breast cancer (e.g. primary breast adenocarcinoma - C50.919, personal history of breast cancer - Z85.3) and renal cancer (e.g kidney neoplasm - D49.519, renal cell carcinoma - C64.9) to search our Epic© patient database for all patients who combined a diagnostic label of breast cancer and renal cancer. For a comprehensive search we used 5,143 breast labels and 1,414 renal labels.

We then chart reviewed the patients and excluded those who did not have both a malignant BC and RCC. Patients with carcinoma-in-situ were included in our sample of patients. Data collected for each patient included their age, gender, personal and family history of cancers, age at cancer diagnoses, histologic subtypes of their BC and RCC, tumor markers, cancer stages at diagnosis, genetic testing done, interventions for breast and renal cancer, and patient outcomes. Patient characteristics were summarized in median for continuous variables, and in frequencies and percentages for categorical variables. Outcomes were labeled as progression, partial response, or complete remission based on RECIST criteria ¹⁶. If a patient developed progression at any point their outcome was labeled as progression. Patients who were cancer-free for 10 years or more were labeled as cured.

3. Results

3a) SEER Population Analysis Results:

During 2000–2016, of 813,477 females with BC, a total of 1,914 later developed RCC (patient characteristics in Table 1). A total of 456 cases (23.82%) of RCC were diagnosed within the first 6 months of BC diagnosis, 179 (9.35%) within 7–12 months, 647 (33.8%) within 1–5 years, and 632 (33.01%) after more than 5 years. The risk of developing RCC following BC was significantly elevated within the first 6 months, 7–12 months, and 1–5 years of a BC diagnosis with standardized incidence ratios (SIRs) of 5.08 (95% CI, 4.62–5.57), 2.09 (95% CI, 1.8–2.42), and 1.15 (95% CI, 1.06–1.24),

respectively (Fig. 1A). Beyond 5 years, the risk was similar to the general population (SIR = 1.01, 95% CI [0.93–1.09]).

On the other hand, during the same period, of 56,200 females with RCC, a total of 1,087 later developed BC (patient characteristics in Table 2), of which 121 (11.13%) were within the first 6 months of the RCC diagnosis, 65 (5.98%) within 7–12 months, 472 (43.42%) within 1–5 years, and 429 (39.47%) were after more than 5 years. The risk of developing BC following RCC was significantly elevated within the first 6 months of RCC diagnosis with an SIR of 1.45 (95% CI, 1.20–1.73), while the risk in other latency periods was not significantly different when compared to the general population (Fig. 1B).

3b – Hospital Population Results

There were 822 patients within our institutional records who had a breast cancer and renal cancer diagnostic label. After reviewing the charts 437 patients were identified to have both breast cancer and renal cell cancer. Patients with other diagnoses such as breast fibroadenomas, or cancers that had metastasized to the kidneys were excluded. Among the 437 patients, 427 (97.71%) were female, and 358 (81.92%) were white (Table 3).

Breast cancer was diagnosed before RCC in 246 (61.5%) of the patients. 152 patients had BC and RCC on the same side (76 on the right side, 76 on the left side), 35 had BC bilaterally, and 16 had RCC bilaterally. No patient had both cancers bilaterally. Among the 437 patients, there were another 142 malignancies such as a colorectal cancer and ovarian cancer diagnosed, and the most common malignancies reported in the patients' family histories were breast cancer (125), colorectal cancer (51), lung cancer (45), and prostate cancer (34) (Table 3). There were 15 confirmed germline mutations/variants of uncertain significance in the patients who underwent genetic testing (Table 4), the most common of which was BRCA1/2 (present in 5 patients).

The most common identified BC stages at diagnosis for these patients was stage IA (16.93%) and stage IIA (11.9%) (Table 5a), but the stage at diagnosis was unavailable for > 56% of the patients. Invasive ductal carcinoma was the most common pathological subtype identified. With regards to treatment, 89.47% underwent a surgical intervention such as a lumpectomy or mastectomy, 45.77% received radiation therapy, 31.81% received chemotherapy, and 38.9% got anti-estrogen or anti-HER2 agents. More than a third of the patients (39.58%) were determined to have been cured of their breast cancer (either by being disease-free for > 10 years or by documentation from their oncologist), and 16.71% were in remission (Table 5a).

As for RCC, the most common confirmed stage at diagnosis was stage I disease (34.78%) but the stage was unknown in 48.28% of cases, and clear cell carcinoma represented 45.54% of cases followed by papillary cell carcinoma (7.55%) and chromophobe cell tumors (4.12%) (Table 5b). More than 90% of the patients underwent a surgical intervention (e.g. complete or partial nephrectomy), 38.92% were cured of RCC and 14.87% were in remission following therapy. At the time of our data collection, 92 (21.05%) of

the patients studied were deceased (Table 3). RCC was the most common identified cause of death (20.65%), and BC accounted for 10.87% of the deaths.

4. Discussion

To our knowledge, this study has the largest scale of both national data and institutional records showing an association between BC and RC. We analyzed the data of more than 3,000 US patients via SEER and 437 patients treated our facility who had a history of both BC and RCC. Based on the results of the SEER population analysis, patients with BC are at a higher risk of being diagnosed with RCC within 5 years of their BC diagnosis, and the risk is highest within the first 6 months. Conversely, RCC patients are also at a higher risk of being diagnosed with BC within 6 months of their RCC diagnosis, but this risk is lower. Notably, these cases occurring within 6 months of each other would be classified as synchronous cancers.

It is unclear why such an association exists. One theory is that there are RCC cases being detected incidentally due to staging imaging done for BC, and that may explain why there is a higher chance of being diagnosed with RCC within the first 6 months following a BC diagnosis. However, this does not account for why there is such an increased number of RCC cases among BC patients. This points to a patient population that is predisposed to both BC and RCC, potentially due to similar risk factors, and possibly due to a common underlying genetic mutation. The fact that the risk declines with time indicates that the development of the second cancer is less likely due to a specific treatment modality of the initial malignancy.

Our exploration of internal records of patients with BC and RCC showed a population that was predominantly female and white, and that the diagnosis of BC tended to precede that of RCC. Patients frequently had personal histories of other malignancies and a family history of cancer, particularly BC. A small number of patients had germline genetic testing from which we identified 15 mutations/variants of uncertain significance, the most common of which was BRCA1/2.

The limitations of our study include its retrospective nature and the absence of some data from the records of a number of our patients. More research is needed to study this association between BC and RCC in particular to explore the potential risk factors contributing to development of these diseases, and ideally more genetic testing should be carried out on this patient population to elaborate on any underlying mutations and genetic variants. Based on our findings though, we conclude that it is important to be aware that patients with BC may be at higher risk of having or developing concomitant RCC and vice versa.

Declarations

Disclosures: No conflicts of interest to disclose

Funding: No funding to disclose

Ethics approval: IRB approval was obtained via our institutional IRB review committee, and informed consent was waived as this was a retrospective study

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Tables

Table 1

Baseline characteristics of SEER female breast cancer patients included in the study (n = 813,477) and those who developed RCC (n = 1,914)

	All female breast cancer patients (%)	Female breast cancer patients who later developed RCC					
		Within 6 months	Within 7–12 months	Within 1–5 years	Within 5–10 years	After more than 10 years	Overall
Overall	813,477 (100)	456	179	647	433	199	1,914 (100)
Age at diagnosis of breast cancer							
< 30 years	4,931 (0.61)	0	0	0	1	0	1
30–39 years	41,409 (5.09)	8	2	5	10	5	30
40–49 years	146,759 (18.04)	40	17	57	48	32	194
50–59 years	203,180 (24.98)	110	38	147	117	67	479
60–69 years	196,165 (24.11)	146	58	215	152	61	632
> 69 years	221,033 (27.17)	152	64	223	105	34	578
Race							
White	652,992 (80.27)	362	152	535	371	163	1,583
Black	87,626 (10.77)	64	17	84	40	31	236
Asian or pacific islander	63,877 (7.85)	26	9	27	20	5	87
American Indian/Alaska Native	3,507 (0.43)	2	1	1	2	0	6
Stage of breast cancer							
Localized	498,732 (61.31)	206	89	441	301	137	1,174

	All female breast cancer patients (%)	Female breast cancer patients who later developed RCC					
		Within 6 months	Within 7–12 months	Within 1–5 years	Within 5–10 years	After more than 10 years	Overall
Regional	254,654 (31.30)	209	79	181	124	60	653
Distant	44,045 (5.41)	39	6	13	6	1	65
Hormonal receptors status							
Positive estrogen and progesterone receptors	499,811 (61.44)	280	99	401	274	120	1,174
Positive estrogen receptors only	88,697 (10.9)	44	22	63	42	19	190
Positive progesterone receptors only	8,932 (1.1)	7	2	6	4	3	22
Negative estrogen and progesterone receptors	136,304 (16.76)	83	39	103	47	16	288
Her2neu status							
Positive	51,989 (6.39)	28	11	25	2	0	66
Negative	273,910 (33.67)	146	70	150	23	0	389
Borderline	7,518 (0.92)	6	1	1	1	0	9
Chemotherapy							
Yes	334,428 (41.11)	215	89	230	156	81	771
No/unknown	479,049 (58.89)	241	90	417	277	118	1,143
Radiotherapy							
Yes	401,178 (49.32)	222	103	333	235	116	1,009
No/unknown	412,299 (50.68)	234	76	314	198	83	905

Table 2

Baseline characteristics of SEER female RCC patients included in the study (n = 56,200) and those who developed breast cancer (n = 1,087)

	All female RCC patients (%)	Female RCC patients who later developed breast cancer					Overall
		Within 6 months	Within 7–12 months	Within 1–5 years	Within 5–10 years	After more than 10 years	
Overall	56,200 (100)	121	65	472	309	120	1,087
Age at diagnosis of breast cancer							
< 30 years	715 (1.27)	0	0	1	0	1	2
30–39 years	2,514 (4.47)	2	1	4	4	1	12
40–49 years	6,900 (12.28)	16	2	46	30	16	110
50–59 years	12,733 (22.66)	25	14	95	82	36	252
60–69 years	14,942 (26.59)	25	23	157	104	42	351
> 69 years	18,396 (32.73)	53	25	169	89	24	360
Race							
White	45,621 (81.18)	97	51	382	256	100	886
Black	6,953 (12.37)	17	10	58	38	14	137
Asian or pacific islander	2,695 (4.8)	4	3	28	15	5	55
American Indian/Alaska Native	525 (0.93)	3	1	4	0	1	9
Stage of breast cancer							
Localized	39,734 (70.7)	83	51	393	271	102	900

	All female RCC patients (%)	Female RCC patients who later developed breast cancer					
		Within 6 months	Within 7–12 months	Within 1–5 years	Within 5–10 years	After more than 10 years	Overall
Regional	7,274 (12.94)	17	11	61	31	14	134
Distant	7,615 (13.55)	17	1	10	4	1	33
Chemotherapy							
Yes	3,211 (5.71)	11	0	5	2	1	19
No/unknown	52,989 (94.29)	110	65	467	307	119	1,068
Radiotherapy							
Yes	2,191 (3.9)	3	0	3	2	1	9
No/unknown	54,009 (96.1)	118	65	469	307	119	1,078

Table 3
Patient Characteristics

Patient Characteristics	Number (%)
Gender	
• Female	427 (97.71)
• Male	10 (2.29)
Median age of patients	76.7
Median age at breast cancer diagnosis	61.0
Median age at RCC diagnosis	65.0
Race	
• White	358 (81.92)
• Black	37 (8.47)
• N/A or declined	35 (8.01)
• Hispanic	4 (0.92)
• American Indian/Alaska Native	2 (0.46)
• Asian	1 (0.23)
Cancer diagnosed first	
• Breast	246 (61.5)
• Renal	122 (30.5)
• Unknown	32 (8.0)
Smoking status	
• Never Smoker	228 (52.17)
• Former Smoker	173 (39.59)
• Current smoker	29 (6.64)
• Unknown	7 (1.6)
Alcohol consumption	137 (31.35)
Personal history of other cancers	
• Colorectal cancer	21 (4.8)
• Lung cancer	19 (4.35)

Patient Characteristics	Number (%)
• Bladder cancer	10 (2.29)
• Endometrial cancer	8 (1.83)
• Ovarian cancer	7 (1.6)
• Upper GI cancers	5 (1.14)
• Prostate cancer	2 (0.46)
• Other cancers (cutaneous, lymphoma, etc)	70 (16)
Family history of cancers	
• Breast cancer	125 (28.6)
• Renal cell cancer	12 (2.75)
• Colorectal cancer	51 (11.67)
• Lung cancer	45 (10.3)
• Prostate cancer	34 (7.78)
• Upper GI cancers	23 (5.26)
• Ovarian cancer	21 (4.81)
• Endometrial cancer	8 (1.83)
• Other cancers	78 (17.85)
Living status	
• Alive	245 (56.06)
• Deceased	92 (21.05)
• Unknown/lost to follow up	100 (22.88)
Cause of death	
• Renal cancer	19 (20.65)
• Breast cancer	10 (10.87)
• Another cancer	4 (4.35)
• Other cause of death	17 (18.48)
• Unknown	42 (45.65)

Table 4
Genetic mutations and variants identified

Germline Mutation / Hereditary Syndrome	Frequency of occurrence
BRCA1	Confirmed mutation: 4 Confirmed negative: 35
BRCA2	Confirmed mutation: 1 Confirmed negative: 36
P53	Confirmed mutation: 2 Confirmed negative: 24 Variant: 1
VHL	Confirmed mutation: 0 Confirmed negative: 20
HNPCC	Confirmed mutation: 0 Confirmed negative: 22
Tuberous sclerosis syndrome (unclear which gene)	1 patient
PTEN mutation (Cowden Syndrome): c.634 + 1G > C	1 patient
VUS* in APC: c.6173G > A (p.Gly2058Asp)	1 patient
VUS in PALB2: c.949A > C (p.Thr317Pro)	1 patient
VUS in PTEN gene: c.159A > G (p.Val53Val)	1 patient
VUS in CDH1: c.2387G > A (p.Arg796Gln)	1 patient
Clinical Cowden Syndrome (no gene mutation identified)	1 patient

Table 5
a - Features of BC ; Table 3b - Features of RCC

Table 5a Breast Cancer Features	Number (percentage)
Breast cancer staging at diagnosis	
• In situ	6 (1.37)
• IA	74 (16.93)
• IB	11 (2.52)
• IIA	52 (11.9)
• IIB	17 (3.89)
• IIIA	10 (2.29)
• IIIB	1 (0.23)
• IIIC	7 (1.60)
• IV	13 (2.97)
• Unknown	246 (56.29)
Breast cancer pathology	
• Invasive ductal carcinoma	164 (37.53)
• Invasive lobular carcinoma	13 (2.97)
• Other (DCIS, LCIS)	39 (8.92)
• Unknown	203 (46.45)
Hormonal receptor expression	
• ER expression	183 (41.88)
o Yes	30 (6.86)
o No	224 (51.26)
o Unknown	
• PR expression	154 (35.24)
o Yes	48 (10.98)
o No	235 (53.78)
o Unknown	
• HER-2 expression	28 (6.41)
o Yes	139 (31.81)
o No	270 (61.78)
o Unknown	
Breast cancer treatment	
• Surgery (lumpectomy, mastectomy)	391 (89.47)

Table 5a Breast Cancer Features	Number (percentage)
• Chemotherapy	139 (31.81)
• Radiation therapy	200 (45.77)
• Hormonal / Anti-Her 2 agents	170 (38.9)
• Immunotherapy	3 (0.69)
• Unknown	29 (6.64)
Breast cancer outcomes	
• Cure	173 (39.58)
• Complete response / remission	73 (16.71)
• Partial response	4 (0.92)
• Progression	39 (8.92)
• Unknown / lost to follow up	127 (29.06)
Table 5b Renal cell carcinoma features	Number (percentage)
RCC staging at diagnosis	
• I	152 (34.78)
• II	22 (5.03)
• III	32 (7.32)
• IV	20 (4.58)
• Unknown	211 (48.28)
RCC histologic subtype	
• Clear Cell Carcinoma	199 (45.54)
• Papillary Cell Carcinoma	33 (7.55)
• Chromophobe Cell Carcinoma	18 (4.12)
• Other	27 (6.18)
• Unknown	160 (36.61)
RCC treatment	
• Surgery (complete/partial nephrectomy)	397 (90.85)
• Chemotherapy	23 (5.26)
• Radiation	15 (3.43)

Table 5a Breast Cancer Features	Number (percentage)
• Targeted agents	14 (3.20)
• Immunotherapy	12 (2.75)
• No therapy / Unknown	28 (6.41)
Outcomes of RCC	
• Cure	174 (38.92)
• Complete Response / Remission	65 (14.87)
• Partial response	4 (0.92)
• Progression	47 (10.76)
• Unknown	147 (33.64)

Figures

A

B

Figure 1

Standardized Incidence Ratio (SIR) of RCC diagnosis after being diagnosed with BC. Figure 1B: SIR of BC diagnosis after being diagnosed with RCC