Clinical and sociodemographic risk factors associated with the development of second primary cancers among postmenopausal breast cancer survivors

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Abstract

Introduction

: Advances in breast cancer (BC) diagnosis and treatment have increased the number of long-term survivors. Consequently, primary BC survivors are at a greater risk of developing second primary cancers (SPCs). The risk factors for SPCs among BC survivors including sociodemographic characteristics, cancer treatment, comorbidities, and concurrent medications have not been comprehensively examined. The purpose of this study is to assess the incidence and clinicopathologic factors associated with risk of SPCs in BC survivors.

Methods

We analyzed 171, 311 women with early-stage primary BC diagnosed between January 2000-December 2015 from the Medicare-linked Surveillance Epidemiology and End Results (SEER-Medicare) database. SPC was defined as any diagnosis of malignancy occurring within the study period and at least six months after primary BC diagnosis. Univariate analyses compared baseline characteristics between those who developed a SPC and those who did not. We evaluated the cause-specific hazard of developing a SPC in the presence of death as a competing risk.

Results

Of the study cohort, 21,510 (13%) of BC survivors developed a SPC and BC was the most common SPC type (28%). The median time to SPC was 44 months. Women who were white, older, and with fewer comorbidities were more likely to develop a SPC. While statins [hazard ratio (HR) 1.066 (1.023–1.110)] and anti-hypertensives [HR 1.569 (1.512–1.627)] increased the hazard of developing a SPC, aromatase inhibitor therapy [HR 0.620 (0.573–0.671)] and bisphosphonates [HR 0.905 (0.857–0.956)] were associated with a decreased hazard of developing any SPC, including non-breast SPCs.

Conclusion

Our study shows that specific clinical factors including type of cancer treatment, medications, and comorbidities are associated with increased risk of developing SPCs among older BC survivors. These results can increase patient and clinician awareness, target cancer screening among BC survivors, as well as developing risk-adapted management strategies.

Introduction

Breast cancer (BC) accounts for nearly one in three cancer cases diagnosed in women (1). Early detection as well as improved management have contributed to the increase in survival rates of BC patients. As a

result, longer life expectancy is accompanied by increased risk of developing a second primary cancer (SPC), defined as malignant tumors with differing pathologic morphologies, and are not metastases from the initial primary cancer (1, 2).

The incidence of SPCs among women with primary BC have been inconclusive, ranging from 4–17%, with varying follow up times (1). Though prior studies show that BC survivors are more susceptible to developing a SPC (3, 4), it has been difficult to quantify that risk, and identify specific factors that may predispose some BC survivors to developing SPCs. The American Cancer Society recommends annual mammography screenings for the general population as well as specific guidelines for those with a family history of BC or women with genetic mutations. However, there is currently not enough evidence for specific BC screening recommendations based on having a personal history of BC. There are also no comprehensive screening guidelines for other types of cancers in BC survivors.

The purpose of this study is to (1) assess the incidence and types of SPCs among an extensive cohort of older BC survivors and (2) identify clinical and sociodemographic factors associated with the development of SPCs. Our study will aid in improving clinician and patient awareness of SPCs in BC survivors and guide discussions for developing risk-adapted management strategies.

Materials And Methods

Data Sources

Study participants were selected from the Surveillance, Epidemiology and End Results registry linked to Medicare claims record (SEER-Medicare). We excluded individuals in healthcare maintenance organizations (HMOs) and those without Medicare Parts A and B insurance, due to incomplete claims which are needed to assess comorbidities and cancer treatment (e.g., surgery, chemotherapy, radiation therapy). We excluded individuals without Medicare Part D claims data which were needed to ascertain prescription medication use.

Study Population

We identified patients > 66 years of age who were diagnosed with primary BC between January 1, 2000, and December 31, 2015, in the SEER-Medicare database. We only included patients with a pathologically confirmed primary BC diagnosis. Those with diagnoses made at autopsy and with death certificate were excluded. We further limited our cohort to include only female patients, with early stage (0 to III) primary BC.

Sociodemographic variables were extracted from Medicare-linked claims and included age at diagnosis, race/ethnicity, income quartile, county/residency type, marital status, first treatment regimen, comorbidities, and medications. Comorbidity burden was assessed using the recommended NCI comorbidity index with weights specific for breast cancer. BC treatment (surgery, chemotherapy, and radiotherapy) was extracted using International Classification of Diseases Ninth Revision (ICD-9), and

Health Care Procedure Coding System (HCPCS) procedural codes. Patients were considered to use the medications of interest (Table 2) if they had used the drug within the year prior to cancer diagnosis until 6 months after diagnosis. Similarly, patients were considered to have specific comorbidities if there was at least one inpatient or two outpatient Medicare claims code for the diagnosis within 1 year prior to cancer diagnosis up until 6 months after primary BC diagnosis. This study was deemed exempt by the Mount Sinai Institutional Review Board.

Study Outcome

The primary outcome was development of any SPC. We excluded diagnosis claims of BC that occurred within six months of the primary BC to remove what were likely multiple primary tumors.

Statistical Analysis

We conducted chi-square tests to evaluate differences in sociodemographic and clinical characteristics of patients with and without SPCs. To estimate the effects of covariates on the rate of SPC occurrence, we used a cause-specific hazard model in the presence of competing risk. The time to development of SPC was defined as the time since the initial BC diagnosis, with a delayed entry of 6 months after the primary BC diagnosis, until SPC occurrence, end of follow-up, or death. The 6-month latency period is in line with SEER Solid Tumor Rules which aims to distinguish single from multiple primary tumors. Patients who experienced death as a competing risk and those who did not develop a SPC were censored. Three cause-specific models were developed: all SPCs, breast only as a SPC, and non-breast SPCs. The results are presented as hazard ratios (HR) with corresponding two-sided 95% confidence intervals (CI). In all models, Her2/neu data was excluded because it was not recorded by the SEER registry for all years evaluated in this study. All statistical analyses were performed using SAS (version 9.4), with the two-sided significance level set at $p < 0.05$.

Results

Final Cohort Characteristics

The final cohort of primary early-stage BC survivors included 171,311 women, with a mean age at diagnosis of 75 years. The median follow-up time was 5 years (interquartile range [IQR]: 6.36). SPC development occurred in 12.6% (n = 21,510) of patients. The total study population consisted of 84% non-Hispanic white, 8% non-Hispanic Black, and 4% Hispanic women. Most of the population lived in urban counties (98%) and 45% were married. The distribution of primary BC stages was: 18% stage 0, 46% stage I, 27% stage II, and 9% stage III. Sixty-eight percent of primary breast tumors were classified as ductal carcinoma. Most tumors were classified as hormone receptor (HR) positive/Her2 negative (79%), and only 9% were triple negative tumors. Surgery occurred in 94% of the population, while 17% underwent chemotherapy, and 40% underwent radiotherapy. Most of the women had an NCI Comorbidity Index score of < 1 (79%). Antihypertensives and statins were the most prescribed medications used by 33% and 20% of the cohort, respectively.

Types of Second Primary Cancers

Of the 21,510 patients who developed a SPC, 28% had a second primary BC (Fig. 2). Lung, colorectal, and urinary cancers comprised 15%, 11%, and 10% of SPC's, respectively. Skin and gynecologic cancers accounted for 6% and 4% of SPCs, respectively. Gallbladder/pancreatic and hematologic cancers each occurred in 4% and 3% of the patient population, respectively. Other SPCs included liver, gastrointestinal, soft tissue and bone, endocrine, and brain, and collectively accounted for 18% of the SPCs. The median time between primary BC and SPC diagnosis was 3.67 years (IQR: 5.09).

Factors associated with the development of SPCs

Unadjusted analysis (Table 1) revealed that SPC cases were more often diagnosed in white patients (12.8% vs. 12.1% among black, 11.6% among Hispanic and 10.2% among other races), those who were somewhat older (13.7% for 70–79 years vs. 12.9% for 66–69 years), and those with fewer comorbidities (12.9% NCI comorbidity index < 1 vs. 12.1% for NCI comorbidity index 1–2 and 10.2% for NCI comorbidity index > 2). Additionally, married BC survivors (12.9% vs. 12.3%) and those in the highest income quartile (12.8% vs. 12.5%) were more likely to develop SPCs. SPCs also occurred more often with stage 0 vs. stage I disease (15.4% vs. 12.8%) and those who underwent surgery (12.7% vs. 9.8%) or radiation therapy (13.5% vs. 11.9%). Chemotherapy was not significantly associated with development of SPC ($p = 0.637$). Additionally, patients who were prescribed medications such as statins, antihypertensives, and thiazolidinediones were more likely to develop a SPC, while those taking aromatase inhibitors were less likely to develop a SPC ($p < 0.001$, Table 2).

In multivariable-adjusted models, the hazard of developing any SPC was greater in patients aged 75–79 [HR 1.121 (1.078–1.165)], highest income quartile [HR 1.066 (1.025–1.108)], and with stage IIIC BC compared to stage 0 [HR 1.169 (1.051–1.300)]. Those who had a greater number of comorbidities [HR 0.735 (0.690–0.784)] had a lower hazard of developing a SPC. However, BC survivors with the following comorbidities had increased hazard of developing any SPC: diabetes [HR 1.363 (1.303–1.426)], renal disease [HR 1.405 (1.333–1.481)], and chronic obstructive pulmonary disease (COPD) [HR 1.760 (1.699–1.824)]. We also observed a lower hazard of SPC in patients who were taking bisphosphonates [HR 0.905 (0.857–0.956)] and aromatase inhibitors [HR 0.620 (0.573–0.671)]. Medications such as anti-hypertensives [HR 1.569 (1.512–1.627)] and statins [HR 1.066 (1.023–1.110)] increased the hazard of SPCs.

In contrast to any SPC, the hazard of developing breast-only SPC was significantly lower in Hispanic BC survivors [HR 0.821 (0.717–0.939)] and higher in those diagnosed with earlier stage BC (stage 0 vs. stage I) [HR 1.434 (1.339–1.536)]. While patients with estrogen receptor (ER) negative status had an increased hazard for BC only SPC [HR 1.442 (1.304–1.595)], patients who received chemotherapy [HR 0.896 (0.820–0.978)] and were taking bisphosphates [HR 0.898 (0.812–0.993)] as well as thiazolidinediones [HR 0.651 (0.496–0.853)] had a significantly lower hazard.

Compared to the breast only SPC group, the factors associated with greater hazard for non-breast SPC were somewhat different. The hazard for non-breast SPCs was highest for patients 75–79 years old [HR 1.187 (1.133–1.243)] compared to those 66–69 years old. Patients who underwent chemotherapy [HR 1.097 (1.043–1.151)] or radiation therapy [HR 1.053 (1.017–1.090)] for their initial primary BC had an increased risk of developing a non-breast SPC. We observed a similar trend for decreased hazard of developing a non-BC SPC in patients who were on medications such as aromatase inhibitors [HR 0.635 (0.581–0.694)] and bisphosphonates [HR 0.892 (0.836–0.952)]. An increased hazard of SPC was observed for those with comorbidities such as diabetes [HR 1.443 (1.369–1.521)], renal disease [HR 1.485 (1.398–1.577) and COPD [HR 2.032 (1.953–2.115)].

Discussion

In this study, we determined the incidence of second primary cancers (SPCs) among early-stage BC survivors and identified several sociodemographic and clinical risk factors associated with the development of SPCs. Using the SEER-Medicare Linked Database with detailed information about Medicare beneficiaries with cancer from 19 United States (US) geographic regions, we found that the incidence of any SPC among older women with primary BC is 13%. Women of white race and those who were married were more likely to develop a SPC. Additionally, hormone receptor (HR) negative primary BC diagnosed at stage 0, treated with surgery or radiotherapy, were also associated with incidence of SPC.

While older age at BC diagnosis (ages 70–79), was associated with increased development of SPC, we observed a decline in SPC incidence among women ≥ 80 years after adjusting for competing risk of death which is consistent with other studies (5). Compared to white women, the incidence of any SPC was lower for women of non-Hispanic black, Hispanic, and other races. The higher incidence of SPC among white women may be due to their overall higher survival rates after BC diagnosis or due to increased surveillance practices (6). It is noteworthy that prolonged survival is an independent risk factor for the development of SPC (7). We also observed that married women were more likely to develop a SPC. Patients who are married are more likely to get psychosocial and financial support which may aid in early cancer detection, appropriate treatment, and prolonged survival (8).

We found that the incidence of all SPCs is higher in those with ductal primary BCs, compared to lobular, as well as in triple negative BC. After adjusting for confounders, primary BC histology was not significantly associated with SPC development, however, estrogen receptor (ER) negative cancers specifically conferred a higher risk of all SPCs. Though most studies tend to focus on combined ER/PR hormone receptor status, it has been found that most BRCA1-associated breast cancers, which are susceptible to recurrence, are ER negative (9). In general, HR negative tumors are more likely to be poorly differentiated with increased recurrence rates (10, 11). The increased recurrence rates may be explained by carcinogenesis research which demonstrated that BC stem cells are HR negative, and thus patients with HR negative tumors are predisposed to cancer early in the breast cell maturation process (12). As such, patients with HR negative breast tumors have a 10-fold increased risk of developing a second hormone negative tumor, as compared to the general population (12).

The current treatment for BC includes surgery, chemotherapy, radiotherapy, and more recently immunotherapy. Most BC survivors in our cohort (94%) received surgery as initial treatment for their primary BC, and surgery was associated with a lower hazard of developing any SPC. This is supported by other studies which showed that patients who did not receive surgery for BC conversely had a higher risk of any SPC including breast (13). Those who received surgery alone (without chemotherapy or radiation therapy) were also at higher risk for developing a contralateral BC (14). This may be due to increased surveillance of the contralateral breast post-BC treatment and suggest that a combination of surgery with or without chemotherapy and radiation therapy is the most effective treatment against BC.

We found that chemotherapy was associated with a decreased risk for breast only SPC, but increased risk of all other SPCs, which is corroborated by studies linking certain chemotherapy drugs with different types of cancers(15, 16). Li et al. reported that SPCs, particularly colon and lung cancers, were higher in patients who received chemotherapy for primary BC, even after adjusting for known confounders (13). Another SEER-based study determined that chemotherapy for BC patients was associated with increased incidence for several SPCs, except for some hematologic malignancies (17). Though the mechanism of how chemotherapy may inadvertently stimulate cancer growth remains largely unclear, it has been shown to be most linked to leukemia and myelodysplastic syndrome (18, 19).

Research regarding the risks of radiation for BC are also generally inconclusive. Some studies have concluded that radiation therapy for BC increases the risk for SPC in the healthy contralateral breast or ipsilateral lung compared to an unexposed population (20). Other studies have shown that only 8% of SPCs are related to radiotherapy (21). Here, we found that similar to chemotherapy, radiation therapy was associated with an increased risk of non-breast SPCs. Although the mechanisms underlying radiation-induced tumorigenesis is unclear, irradiation of surrounding tissues may cause secondary malignancies of these tissues particularly the lungs which was the second highest SPC in our cohort.

Finally, we observed significant associations between certain medications and the development of SPCs. Statins and anti-hypertensives were both associated with increased hazard of developing any SPC including breast SPC, A large population-based study determined that certain antihypertensives, including loop and thiazide diuretics, were associated with adverse BC outcomes, such as increased risk of breast SPCs, recurrence, and BC mortality (22, 23). Thiazide diuretics specifically are associated with insulin resistance, which has been found to be an established risk factor for BC and may also explain the risk associated with antihypertensives (22). While the biological mechanisms are unclear, statins have also been shown to impact cancer outcomes, with varying results for different cancer types. For example, a SEER-based study determined that statin use improved overall and lung cancer specific survival in patients with stage IV non-small cell lung cancer (NSCLC), citing in vitro studies that have demonstrated reduced proliferation, migration, and increased apoptosis of lung cancer cell lines with simvastatin use (24). Prior studies have also explored the use of metformin in cancer treatment, as it has been shown to have a potential antitumor effect (25, 26), though it was not significantly associated with decreased risk of SPCs in our multivariable adjusted models.

Bisphosphonates and aromatase inhibitors were associated with decreased hazard of developing any SPC including non-breast SPCs. Bisphosphonates have been shown to decrease risk of both locoregional/distant BC recurrence or second primary BC (27). Its effect on the development of other SPCs is less well understood. However, anti-tumor properties have been shown in preclinical studies(28) and it is effective in reducing the risk of bone metastases (27). Aromatase inhibitor therapy is the gold standard for the treatment of HR positive BC in post-menopausal BC survivors (29). Preclinical studies have shown that aromatase inhibitors in combination with standard cisplatin chemotherapy for NSCLC decreases tumor progression (24). Post-menopausal hormone exposure was also associated with a reduced risk for later development of NSCLC in the general population (30).

Limitations

This study has some limitations. First, it is possible that certain SPCs may have been recurrence or metastases of primary BC. However, this was mitigated by excluding patients for whom the SPC was a BC diagnosed within six months of the primary BC diagnosis. In our adjusted analyses we also modeled all SPCs, breast only SPCs, and non-breast SPCs to isolate the effects of treatment and medications on the development of SPCs. Our cohort was limited to postmenopausal women; thus, our findings are not necessarily generalizable to premenopausal women. Postmenopausal women are at an increased risk of SPCs due to increasing age and comorbidities. As such, our results can assist in determining those who may benefit from increased cancer surveillance. We were unable adjust for other potential confounders, such as family history of cancer, and reproductive or lifestyle factors such as smoking or obesity. Finally, we do not have detailed treatment information such as type of chemotherapy or radiation therapy dose.

Conclusion

In summary, SPCs pose a threat to BC survivors, though the nuances in potential biologic and epidemiologic explanations remain unclear. Our comprehensive exploration uncovered several risk-based factors such as tumor stage, histology, medications, and comorbidities that can provide guidance to clinicians for cancer screening and prevention among postmenopausal BC survivors.

Declarations

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Competing Interests

The authors Stacyann Bailey, Charlotte Ezratty, Grace Mhango, and Jenny Lin *have no relevant financial or non-financial interests to disclose.*

Data Availability

The data that support the findings of this study are available from NCI SEER-Medicare, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of NCI SEER-Medicare.

Ethics Approval

This study was deemed exempt by the Mount Sinai Institutional Review Board.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Stacyann Bailey, Charlotte Ezratty and Grace Mhango. The first draft of the manuscript was written by Stacyann Bailey, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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31. **Statements and Declarations**

Tables

Table 1
Demographic and Clinical Characteristics associated with Development of Second Primary Cancer

Patient Characteristics (N, %)	Second Primary Cancer Development N = 21510	No Second Primary Cancer Development N = 149801	P-value
Age			
66–69	5147 (12.9)	34634 (87.1)	< 0.001
70–74	6225 (13.7)	39224 (86.5)	
75–79	5364 (13.7)	33690 (86.8)	
>80	4774 (10.2)	42263 (90.6)	
Race/Ethnicity			
White	18316 (12.8)	124813 (87.6)	< 0.001
Black	1595 (12.1)	11545 (88.2)	
Hispanic	794 (11.6)	6319 (89.2)	
Other	805 (10.2)	7124 (90.1)	
Geographic status			
Urban	21091 (12.6)	146827 (87.8)	0.514
Rural	385 (12.1)	2778 (88.4)	
Income quartile			
First quartile	5272 (12.5)	37016 (88.1)	0.390
Second quartile	5365 (12.5)	37515 (88.0)	
Third quartile	5403 (12.6)	37381 (88.0)	
Fourth quartile	5442 (12.8)	36980 (87.2)	
Marital Status			
Married	9841 (12.9)	66642 (87.3)	< 0.001
Not married	11669 (12.3)	83159 (88.2)	
Tumor Stage			
Stage 0	4648 (15.4)	25601 (84.9)	< 0.001
Stage I	10015 (12.8)	68494 (87.6)	
Stage II	5335 (11.4)	41539 (89.0)	

Patient Characteristics (N, %)	Second Primary Cancer Development N = 21510	No Second Primary Cancer Development N = 149801	P-value
Stage III	33 (6.6)	469 (94.0)	
Stage IIIA	753 (10.4)	6479 (90.0)	
Stage IIIB	344 (8.5)	3728 (92)	
Stage IIIIC	382 (9.9)	3491 (91.9)	
Tumor Histology			
Ductal	14571 (12.4)	102546 (87.9)	< 0.001
Lobular	1967 (11.8)	14723 (88.3)	
Other	4972 (13.2)	32532 (87.1)	
Estrogen Receptor Status			
ER+	14675 (11.6)	111440 (88.6)	< 0.001
ER-	2821 (12.5)	19822 (88.0)	
Progesterone Receptor Status			
PR+	12334 (11.6)	93917 (88.7)	0.009
PR-	4901 (12.1)	35604 (88.3)	
Her2 Receptor Status			
Her2+	274 (4.9)	5350 (95.1)	0.156
Her2-	2339 (5.3)	41621 (94.5)	
Breast Subtype			
Her2+/HR+	188 (4.7)	3775 (95.2)	0.303
Her2+/HR-	86 (5.2)	1561 (94.7)	
Her2-/HR+	2077 (5.3)	37229 (94.5)	
Triple Negative	260 (5.7)	4331 (94.5)	
Surgery			
Yes	20407 (12.7)	140397 (87.6)	< 0.001
No	1103 (9.8)	9404 (90.2)	

Patient Characteristics (N, %)	Second Primary Cancer Development N = 21510	No Second Primary Cancer Development N = 149801	P-value
Chemotherapy			
Yes	3620 (12.5)	25404 (87.9)	0.637
No	17890 (12.6)	124397 (87.8)	
Radiotherapy			
Yes	9319 (13.5)	59824 (86.9)	< 0.001
No	1219 (11.9)	89977 (88.4)	
NCI Comorbidity Index			
<1	17422 (12.9)	117801 (87.5)	< 0.001
1–2	2538 (12.1)	18366 (88.1)	
>2	1550 (10.2)	13634 (90.2)	

Table 2
Medications associated with the development of second primary cancers among primary breast cancer survivors

Medication	Second Primary Cancer Development, (N = 20, 838)	No Second Primary Cancer Development, (N = 149, 801)	P-value
Statins, N (%)	4808 (22.3)	29349 (19.6)	< 0.001
Antihypertensive, N (%)	8088 (37.6)	47988 (32.0)	< 0.001
Bisphosphonates, N (%)	1521 (7.1)	9300 (6.2)	< 0.001
Aromatase Inhibitor, N (%)	679 (3.2)	10523 (7.0)	< 0.001
Metformin, N (%)	1291 (6.0)	7636 (5.1)	< 0.001
Insulin, N (%)	624 (2.9)	3779 (2.5)	0.001
Thiazolidinediones, N (%)	238 (1.1)	1337 (0.9)	0.002
SGLT-2 Inhibitors, N (%)	3 (0.01)	110 (0.1)	0.002
DPP-4 Inhibitors, N (%)	278 (1.3)	1793 (1.2)	0.23
GLP-1 Agonists, N (%)	38 (0.2)	236 (0.2)	0.51

Table 3
Multivariable Cox proportional cause-specific hazard models to evaluate the effects of covariates on the rate of second primary cancer development among primary breast cancer survivors.

Patient Characteristic	All SPCs HR (95% CI)	Breast Only SPCs* HR (95% CI)	Non-Breast SPCs* HR (95% CI)
Age (yrs) (REF = 66–69)			
70–74	1.078 (1.038–1.118)*	0.990 (0.926–1.059)	1.117 (1.068–1.168)*
75–79	1.121 (1.078–1.165)*	0.957 (0.891–1.029)	1.187 (1.133–1.243)*
≥ 80	1.056 (1.012–1.101)*	0.820 (0.757–0.888)*	1.127 (1.072–1.184)*
Race/Ethnicity			
White	REF	REF	REF
Black	0.952 (0.903–1.005)	1.071 (0.972–1.179)	0.907 (0.851–0.967)*
Hispanic	0.832 (0.774–0.893)*	0.821 (0.717–0.939)*	0.819 (0.752–0.891)*
Other	0.799 (0.745–0.859)*	0.823 (0.723–0.936)*	0.776 (0.712–0.845)*
Marital Status			
Married	0.985 (0.957–1.013)	1.035 (0.982–1.091)	0.969 (0.938–1.002)
Income Quartile			
First (Lowest)	REF	REF	REF
Second	1.023 (0.984–1.063)	1.036 (0.963–1.114)	1.020 (0.975–1.067)
Third	1.047 (1.007–1.088)*	1.084 (1.008–1.167)*	1.034 (0.988–1.082)
Fourth (Highest)	1.066 (1.025–1.108)*	1.095 (1.017–1.179)*	1.057 (1.010–1.107)*
Geographic Residence (REF = urban)			
Rural	0.943 (0.852–1.044)	0.997 (0.826–1.204)	0.921 (0.816–1.040)
Breast Cancer Stage			

[¥]Insufficient number of observations

Patient Characteristic	All SPCs HR (95% CI)	Breast Only SPCs* HR (95% CI)	Non-Breast SPCs* HR (95% CI)
Stage I	REF	REF	REF
Stage 0	1.094 (1.052–1.138)*	1.434 (1.339–1.536)*	0.948 (0.903–0.995)*
Stage II	0.999 (0.964–1.035)	0.886 (0.825–0.952)*	1.031 (0.989–1.073)
Stage III	0.845 (0.599–1.191)	1.156 (0.637–2.098)	0.725 (0.476–1.103)
Stage IIIA	1.009 (0.934–1.091)	0.827 (0.699–0.979)*	1.054 (0.966–1.151)
Stage IIIB	1.076 (0.963–1.202)	1.081 (0.864–1.353)	1.052 (0.926–1.196)
Stage IIIC	1.169 (1.051–1.300)*	1.262 (1.029–1.549)*	1.123 (0.992–1.271)
Tumor Histology			
Ductal	REF	REF	REF
Lobular	0.972 (0.926–1.019)	1.133 (1.037–1.237)*	0.914 (0.864–0.968)*
Other	1.023 (0.990–1.057)	1.085 (1.022–1.153)*	1.003 (0.964–1.043)
ER Status (REF = ER Positive)			
ER Negative	1.130 (1.071–1.192)*	1.442 (1.304–1.595)*	1.032 (0.969–1.100)
PR Status (REF = PR Positive)			
PR Negative	0.996 (0.954–1.040)	0.971 (0.892–1.058)	1.006 (0.957–1.058)
Comorbidity Index			
0.00–1.00	REF	REF	REF
1.01–2.00	0.780 (0.738–0.824)*	0.701 (0.629–0.781)*	0.779 (0.730–0.830)*
> 2.00	0.735 (0.690–0.784)*	0.697 (0.612–0.794)*	0.699 (0.649–0.812)*
Comorbidities			

¥Insufficient number of observations

Patient Characteristic	All SPCs HR (95% CI)	Breast Only SPCs* HR (95% CI)	Non-Breast SPCs* HR (95% CI)
Diabetes	1.363 (1.303–1.426)*	1.277 (1.168–1.369)*	1.443 (1.369–1.521)*
Renal Disease	1.405 (1.333–1.481)*	1.320 (1.183–1.474)*	1.485 (1.398–1.577)*
Chronic Obstructive Pulmonary Disease	1.760 (1.699–1.824)*	1.223 (1.132–1.321)*	2.032 (1.953–2.115)*
Cancer Treatment			
Surgery	0.743 (0.698–0.791)*	0.714 (0.636–0.802)*	0.753 (0.699–0.812)*
Radiation Therapy	1.024 (0.995–1.055)	0.980 (0.928–1.036)	1.053 (1.017–1.090)*
Chemotherapy	1.031 (0.987–1.078)	0.896 (0.820–0.978)*	1.097 (1.043–1.154)*
Medications			
Aromatase Inhibitor	0.620 (0.573–0.671)*	0.467 (0.393–0.554)*	0.635 (0.581–0.694)*
Statins	1.066 (1.023–1.110)*	1.131 (1.048–1.221)*	1.055 (1.005–1.108)*
Anti-hypertensives	1.569 (1.512–1.627)*	1.978 (1.845–2.120)*	1.530 (1.464–1.598)*
Bisphosphonates	0.905 (0.857–0.956)*	0.898 (0.812–0.993)*	0.892 (0.836–0.952)*
Metformin	1.054 (0.986–1.127)	1.041 (0.915–1.185)	1.072 (0.992–1.159)
Insulin	0.908 (0.898–1.071)	1.097 (0.926–1.300)	0.944 (0.851–1.047)
Thiazolidinediones	0.816 (0.714–0.931)*	0.651 (0.496–0.853)*	0.870 (0.748–1.013)
SGLT2-Inhibitors	0.388 (0.125–1.206)	0.000 (0.000-1.55E39)¥	0.470 (0.151–1.464)
DDP4-Inhibitors	1.057 (0.933–1.197)	1.208 (0.955–1.529)	1.043 (0.900–1.208)
GLP1-Agonists	1.289 (0.932–1.784)	1.265 (0.690–2.320)	1.311 (0.892–1.927)

¥Insufficient number of observations

Figures

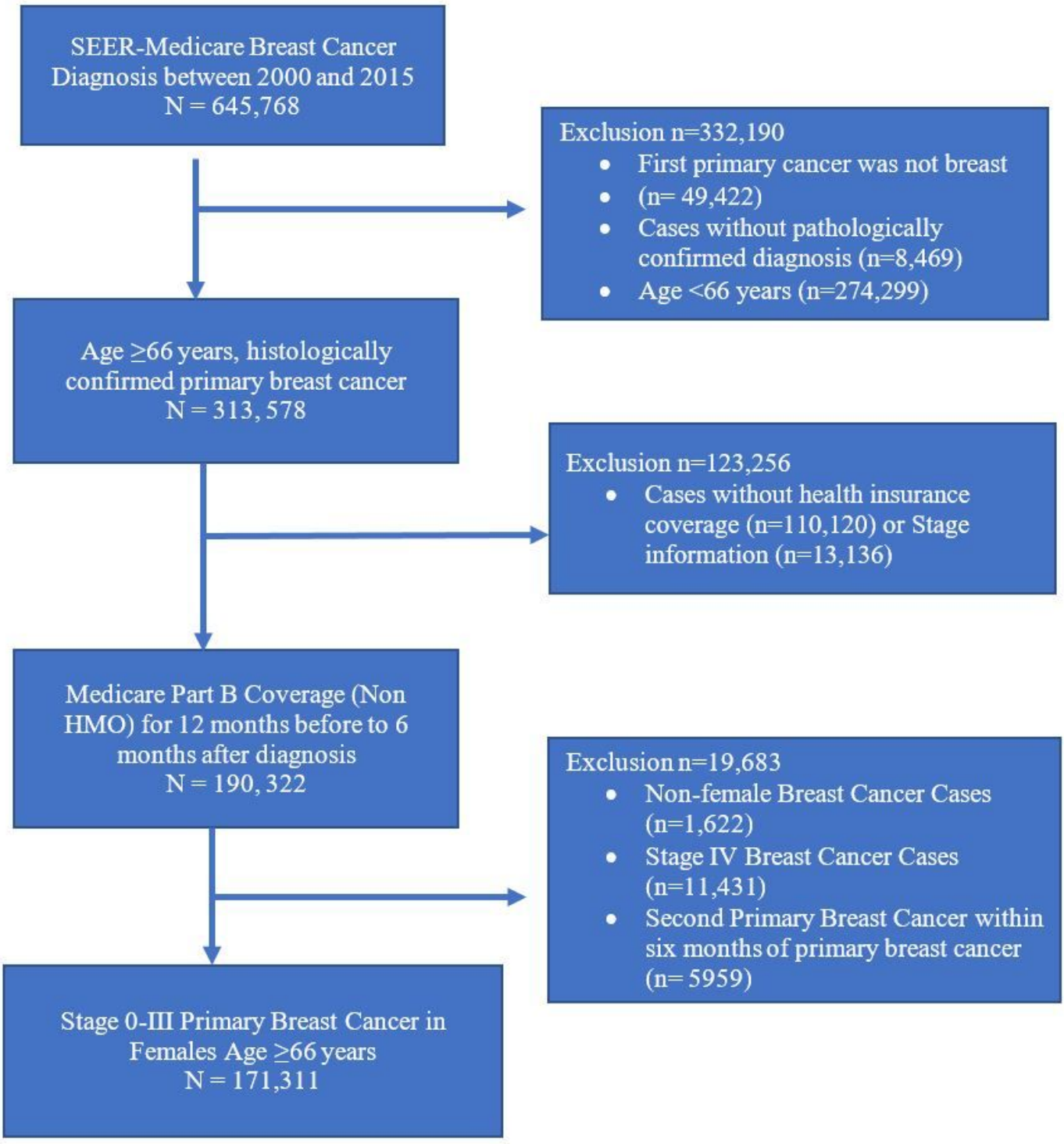

Figure 1

Summary of the final cohort selection. HMO = health maintenance organization; Part B= supplemental insurance

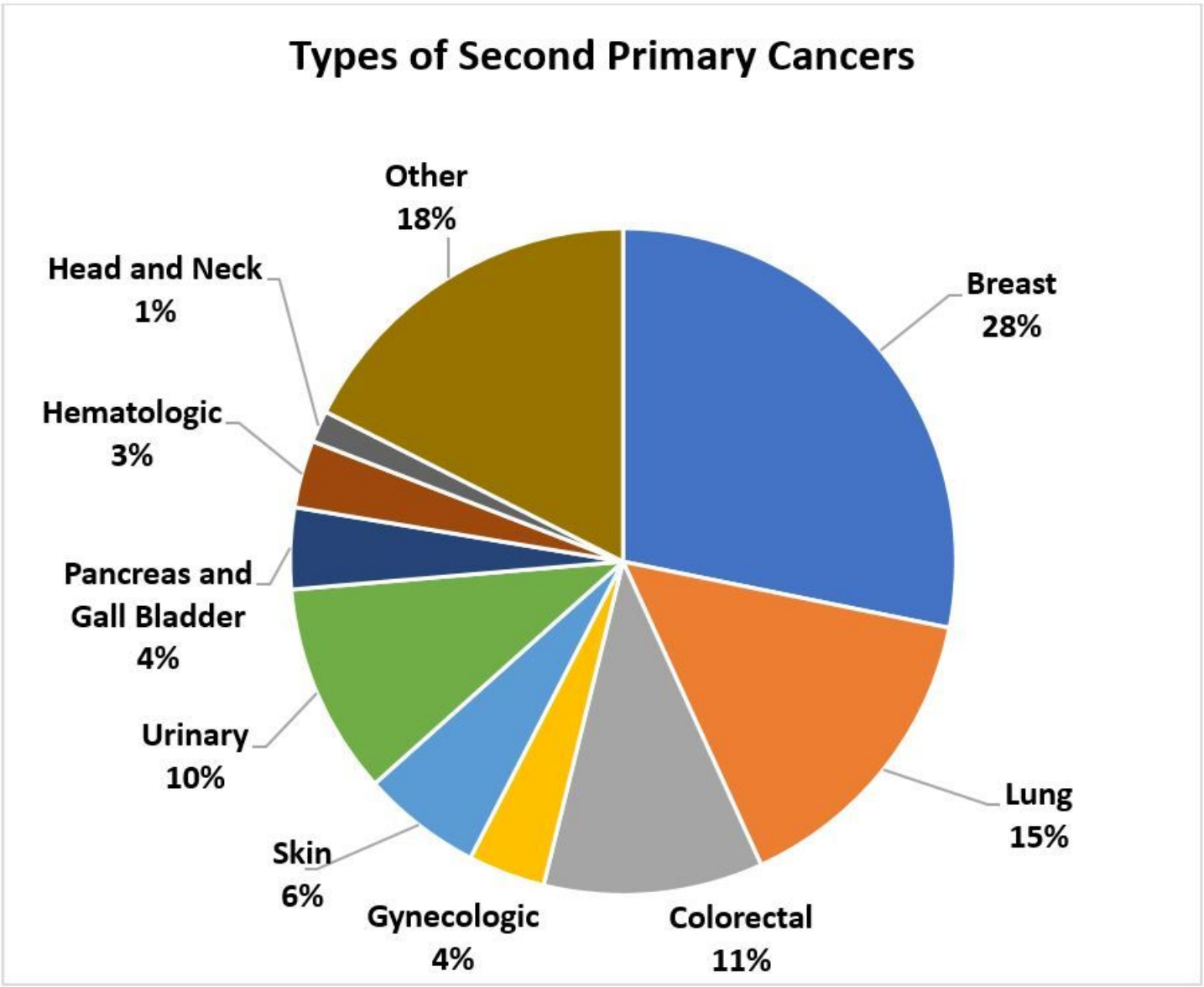

Figure 2

Types of second primary cancers among primary breast cancer patients. Other includes Liver, GI, Soft Tissue, Bone, Endocrine, Brain and CNS, and other