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Increased Risk of Arterial Thromboembolism in Older Men with Breast Cancer

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Abstract

Purpose—Male breast cancer is a rare and understudied disease predominantly affecting men over age 60. Risk of arterial thromboembolic events (ATE) in men increases with age. We examined ATE risk following primary breast cancer diagnosis in elderly men.

Methods—Men with primary breast cancer diagnoses from 2002 to 2011 were identified using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Cases were individually matched by age, sex, race, registry, and comorbidities to controls without cancer using SEER-Medicare's 5% non-cancer sample. Medicare claims were used to identify ATE, defined as myocardial infarction or ischemic stroke. Cumulative incidence of ATE was calculated using competing risk methodology, with death considered a competing event. Cox proportional hazards analysis was used to compare rates of ATE among cases and controls.

Results—Three months following primary breast cancer diagnosis, ATE risk in the cohort of 881 men was 80% higher than matched controls (Hazard Ratio, 1.8; 95% Confidence Interval, 1.0–3.2). Six months post-cancer diagnosis, 5.7% of cases had experienced ATE whereas only 3.5% of controls had (Hazard Ratio, 1.6; 95% Confidence Interval, 1.0–2.6). ATE risk remained elevated 12 months post-cancer diagnosis. Among cases, risk of death was three-fold higher in men who developed ATE.

Conclusions—We provide population-based evidence that male breast cancer patients have a substantially elevated risk of ATE in the first year following a cancer diagnosis as compared to matched controls. Providers should consider this heightened risk when evaluating cardiovascular health in men with a recent breast cancer diagnosis.

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Keywords

Male breast cancer; population-based; SEER; Medicare; arterial thromboembolism; rare cancer

Background

Male breast cancer accounts for approximately 1% of all breast cancer cases diagnosed in the United States.¹ Because breast cancer in men is rare, clinical data are often obtained from small case studies or extrapolated from what is known regarding female breast cancer. However, male breast cancer represents a unique disease with different epidemiologic, genetic, and biologic characteristics.^{2–5}

Each year, roughly 800,000 people experience a stroke in the United States, of which 87% are ischemic. The incidence of ischemic stroke increases with age and varies by gender.⁶ Myocardial infarction (MI), another common form of arterial thromboembolism, disproportionately affects the elderly and has a higher incidence in men. There are an estimated 200 MIs per 100,000 person-years annually with a mean age at presentation of 69, and 62% occur in men.⁷

In a prior study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we demonstrated an increased risk of stroke in patients with common solid tumor cancers.⁸ Zoller and colleagues also established heightened risk of stroke and coronary artery disease following cancer diagnosis in a population-based setting.^{9,10} Although previous research indicates an increased risk of cerebrovascular and cardiovascular events following a breast cancer diagnosis, risk of arterial thromboembolic events (ATE) in elderly men with breast cancer has not been described. This is the first study, to our knowledge, examining the risk of ATE following a primary breast cancer diagnosis in elderly men.

Methods

Design

This was a population-based, matched cohort study using Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims from 2002 through 2012. The SEER registries include over 25% of all patients diagnosed with cancer in the United States. Medicare is the primary health insurer for Americans 65 years and older and covers medical care including, but not limited to, inpatient hospital treatment, outpatient care, and physician services. The SEER-Medicare linked database is a unique resource offering a large population-based cohort which can be used to longitudinally evaluate health outcomes.¹¹ SEER also provides data from a 5% random sample of Medicare beneficiaries without cancer residing in SEER geographic regions and the Medicare files available for the 5% random sample control group are identical to those available for cancer cases. This permitted a framework to compare the risk of ATE in male patients with breast cancer versus matched patients without cancer. We utilized Medicare claims from the physician and supplier file, outpatient standard analytic file, and the provider analysis and review file. Claims were available through December 31, 2012, which was the end of follow-up for our study design.

The Memorial Sloan Kettering institutional review board deemed this study exempt from review and waived the need for informed consent.

Cancer Cohort

Using the latest release of the data, we identified our cohort using the SEER-Medicare linked databases from January 1, 2002 to December 31, 2011. We selected men diagnosed with a first primary breast cancer from the SEER Patient Entitlement and Diagnosis Summary file (PEDSF) utilizing the `siterwho1` variable (Breast: 26000). Exclusions were made if any of the following occurred: patient lacked Part A or B Medicare coverage or belonged to a health maintenance organization in the year prior to breast cancer diagnosis or through follow-up; breast cancer diagnosis was made at the time of death, by autopsy, or death certificate only; month of breast cancer diagnosis was missing; breast cancer diagnosis was not the first primary cancer diagnosis; breast cancer diagnosis was made before age 66; a Medicare claim for MI or ischemic stroke was observed in the year prior to the case's breast cancer diagnosis; or a control could not be identified for matching purposes described in further detail below. Sociodemographic characteristics, including age at breast cancer diagnosis, race, year of breast cancer diagnosis, marital status, dwelling type, and census tract poverty level, were available in the SEER PEDSF file.

Matched Controls

Controls were selected from the 5% sample of Medicare beneficiaries residing in SEER registries without cancer. Male primary breast cancer cases were individually-matched to controls on the following factors: exact birth year, SEER registry geographic region (South: Louisiana, Kentucky, Georgia; Northeast: Connecticut, New Jersey; Midwest: Utah, New Mexico, Iowa, Detroit; and West: Hawaii, California, and Seattle, Washington), race (white or nonwhite), Charlson comorbidity score in the year prior to the case's breast cancer diagnosis (0 or 1+), and atrial fibrillation or hypertension in the year prior to the case's breast cancer diagnosis (yes for either or no for both). The Charlson comorbidity score is an index of comorbid conditions including, but not limited to, chronic lung disease, diabetes, liver disease, and heart disease.¹² Claim codes used for matching included atrial fibrillation (427.31, 427.32) and hypertension (401–405, 437.2). Controls were not eligible to be matched if they were female or if they lacked Medicare Part A or B coverage or were enrolled in a health maintenance organization in the year prior to the matched case's breast cancer diagnosis or during follow-up. Controls were also excluded if a Medicare claim for MI or ischemic stroke was observed in the year prior to the matched case's breast cancer diagnosis.

Measurements

The main outcome of interest was ATE defined as either an inpatient or outpatient claim for MI (410.x) or ischemic stroke (433.x1, 434.x1, or 436). Utilizing the validated Tirschwell method, a claim for ischemic stroke was not considered a main outcome of interest if there was a concurrent claim code for rehabilitation (V57) in the primary diagnosis position or trauma (800–804, 850–854) or hemorrhagic stroke (430, 431) in any diagnosis position.¹³ Secondary outcomes of interest were MI alone and ischemic stroke alone. Medicare claims data has been previously shown to be useful for identifying stroke events with algorithm

performance of 86% positive predictive value.¹⁴ The ICD-9-CM code 410.x has 94% positive predictive value for the WHO definition of acute myocardial infarction when compared to detailed chart review.¹⁵

Statistical Analysis

Simple statistic measures such as means, standard deviations, and frequencies were used to describe the cohort with regard to demographic and tumor characteristics. Time to ATE was analyzed using competing risks methodology where ATE was the event of interest and death due to any cause without a claim for ATE was the competing event. Follow-up time was calculated from date of breast cancer diagnosis to date of whichever came first: ATE, death, or date of last administrative follow-up (Medicare claims information was available through December 31, 2012). Cumulative incidence and hazard ratios (HRs) with their respective 95% confidence intervals (CIs) were calculated at 3 months, 6 months, 1 year, 2 years, and 3 years following breast cancer diagnosis. Cumulative incidence curves of ATE by breast cancer status were utilized to inspect results visually. Overall survival (OS) was calculated from the date of the matched patient's breast cancer diagnosis until death for those who died or until end of study for those who were censored. To examine the effect of ATE on mortality, a time-dependent Cox model was built for cancer cases only, adjusting for all matching factors and the American Joint Committee on Cancer (AJCC) stage at diagnosis.¹⁶ All statistical analyses and graphics were done in SAS (version 9.4, Cary, NC) and R (version 3.2.4, the R Foundation for Statistical Computing).

Exploratory Analysis

In an exploratory analysis, we compared the incidence of Medicare claims for obesity (278.0, 278.00, 278.01) and depression (296.2, 296.20, 296.3, 296.30, 300.4, 309.1, 311) in the year prior to study entry in men with and without breast cancer using the Chi-squared test.

Results

Patient Characteristics

A total of 881 men were matched to non-cancer controls. The mean age at cancer diagnosis was 77 years and the majority of men were diagnosed with stage I or II disease (Table 1). Most matched pairs were white (85%) and 42% had at least one comorbidity defined by the Charlson Comorbidity Index in the year prior to the matched case's cancer diagnosis. The median overall survival (OS) for cases was 5.8 years (95% CI, 5.0–6.5) and for controls the median OS was 9.1 years (95% CI, 8.4–10.1). There was no difference in the incidence of obesity ($p=0.57$) or depression ($p=0.23$) in the year prior to study entry between men with and without breast cancer.

Primary Endpoint: ATE

In the first three months following a first primary breast cancer diagnosis, men had a cumulative incidence of ATE of 3.4% (95% CI, 2.2–4.6) whereas controls had an incidence of ATE of 1.9% (95% CI, 1.0–2.8) (Table 2). The hazard ratio at three months for ATE incidence comparing cancer patients to matched controls was 1.8 (95% CI, 1.0–3.2). This

increase in risk was sustained through six months of follow-up and even at one year the difference was notable (HR: 1.4; 95% CI, 1.0–2.0). By two years, the risk of ATE had decreased but remained slightly, albeit nonsignificantly, elevated (Figure 1).

Secondary Endpoint: MI

In the first three months following primary breast cancer diagnosis, men had a cumulative incidence of MI of 1.8% (95% CI, 0.9–2.7) compared to a cumulative incidence of MI of 1.0% (95% CI, 0.4–1.7) for matched controls without cancer (Table 3). This relative difference was maintained through 6 months post-cancer diagnosis but resolved at one year. HRs were not statistically significant.

Secondary Endpoint: Ischemic Stroke

In the first three months following primary breast cancer diagnosis, men had a cumulative incidence of 1.6% for ischemic stroke (95% CI, 0.8–2.4) compared to 1.1% (95% CI, 0.4–1.8) for matched controls without cancer (Table 4). This relative difference was maintained through three years post-cancer diagnosis, although HRs were not statistically significant.

Mortality

Finally, in a case-only analysis, we investigated the effect of ATE on mortality. Adjusting for matching factors and AJCC stage at time of breast cancer diagnosis, we found an increased risk of death for men with an ATE versus men without (HR, 3.1; 95% CI, 2.5–3.8).

Discussion

This is, to our knowledge, the first study to examine the risk of ATE following a primary breast cancer diagnosis in elderly men. We found that the risk of ATE in elderly men was increased 60% at 6 months following a first breast cancer diagnosis as compared to individually-matched controls without cancer. Although this risk declined over time, even at two years following a breast cancer diagnosis, ATE risk remained slightly elevated.

Population-based studies have shown increased risks of stroke and coronary heart disease following cancer diagnosis of many sites,^{8–10} although male breast cancer has never been described, despite the higher risk of ATE disease in older men even without cancer as a comorbidity. Previously we found in the first three months following an elderly breast cancer diagnosis, patients, 99% of whom were women, had a 1.5% cumulative incidence of stroke compared to 1.1% in matched controls without cancer.⁸ Zoller et al reported a six-month standardized incidence ratio (SIR) for ischemic stroke of 1.5 in patients with breast cancer compared to controls without cancer;⁹ and similarly, a SIR of 1.3 for coronary artery disease.¹⁰ Our main outcome of interest was a composite of ischemic stroke and MI, and our results are bolstered by the fact that the relative difference we found between elderly male breast cancer cases and matched controls was similar in direction and strength to those previously published for breast cancer overall.^{8–10}

Cancer, particularly adenocarcinoma histology, can induce a hypercoagulable state.^{17,18} Malignant cells can produce procoagulant factors or stimulate endothelial cells, platelets,

and monocytes to form clot.¹⁹ Cancer-associated hypercoagulation has been demonstrated to contribute to the etiology of stroke in patients with cancer.²⁰ Other cancer-associated risk factors for stroke such as vessel infiltration and compression, as well as immobilization, have also been identified.²⁰ Patients with cancer frequently undergo invasive procedures, which typically require a temporary interruption in preventative anti-thrombotic medicines. Surgery can also increase the risk of thromboembolism by activating the hemostatic system.¹⁹ Furthermore, negative direct and indirect cardiovascular effects of cancer treatment (chemotherapy, targeted agents, radiation, and hormonal therapy) have been established in both observational and clinical trial studies.^{21,22} Cardiotoxicity in elderly women with breast cancer treated with anthracyclines and trastuzumab is particularly well-documented.^{23–26} In line with this, the National Comprehensive Cancer Network (NCCN) has published guidelines regarding cardioprotective measures for breast cancer survivors, especially for those who received anthracycline-based chemotherapeutic treatment, noting that cardiotoxic events can take years to manifest.²⁷ In the current study, we found an immediate increased risk of ATE following a male breast cancer diagnosis, which had not fully resolved three years after cancer diagnosis. These data suggest that male breast cancer patients may be at heightened risk for thromboembolism in both the acute and chronic settings.

MI and ischemic stroke are leading causes of death worldwide; consequently, identifying people at risk for these diseases is paramount. Bradshaw and colleagues reported that breast cancer survivors are at increased risk for cardiovascular disease-related mortality compared to women without breast cancer.²⁸ In the current study we found that men older than age 65 with breast cancer were almost twice as likely as their matched counterparts without cancer to experience an ATE in the immediate months following their cancer diagnosis. Furthermore, we found that among cancer cases, having an ATE increased the risk of death three-fold. Thus, we have identified a group of patients who would likely benefit from immediate education, surveillance, and preventative measures.

Our study has some limitations. First, the linked SEER-Medicare databases do not provide information on several, granular cardiovascular risk factors, including body mass index, smoking, and family history of thromboembolism. Furthermore, the administrative nature of these datasets prevents us from providing information on the type, severity, and mechanism of ATE outcomes. Second, the relatively small number of outcomes precludes investigation regarding the effects of cancer treatment such as surgery, radiation, and chemotherapy, as well as cancer stage on risk of ATE, and, furthermore, the limited data availability for Part D claims precludes investigation regarding the effects of hormone therapy on ATE risk. Third, these results are, by design, applicable only to men aged 66 years and older. However, our results come from national population-based data that covers approximately 30% of the United States population. In addition, 93% of SEER patients over age 65 have linked Medicare claims data, suggesting our findings are robust and widely applicable to the population we studied.^{11,29}

Conclusions

Utilizing the linked SEER-Medicare database, we conducted the first population-based study investigating the risk of ATE among elderly men with primary breast cancer. We found that men with new diagnoses of breast cancer face a 60% increased risk of ATE in the first 6 months after diagnosis as compared to demographic- and comorbidity-matched controls without cancer. This risk decreased over time, but remained modestly elevated two years after cancer diagnosis. Among cases, we found a threefold increased risk of death for men with an ATE versus men without. Our study illustrates the importance of cardiovascular health management and risk reduction strategies following a breast cancer diagnosis in older men.

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List of abbreviations

ATE	Arterial Thromboembolic Event
SEER	Surveillance, Epidemiology, and End Results
MI	Myocardial Infarction
PEDSF	Patient Entitlement and Diagnosis Summary File
HR	Hazard Ratio
CI	Confidence Interval
OS	Overall Survival
AJCC	American Joint Committee on Cancer
SIR	Standardized Incidence Ratio
NCCN	National Comprehensive Cancer Network
SD	Standard Deviation
HTN	Hypertension
AF	Atrial Fibrillation

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Figure 1.
Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in male breast cancer patients compared to matched controls

Table 1

Demographics and clinical characteristics of SEER-Medicare male breast cancer patients and their matched controls, 2002–2011.

Characteristic	Male Breast Cancer Patients (N=881)	Controls without Cancer (N=881)
Age, mean (SD), years	77 (7)	77 (7)
Race		
White	752 (85%)	752 (85%)
Nonwhite	129 (15%)	129 (15%)
Registry region ^a		
South	188 (21%)	188 (21%)
Northeast	221 (25%)	221 (25%)
Midwest	148 (17%)	148 (17%)
West	324 (37%)	324 (37%)
Charlson Comorbidities		
0	507 (58%)	507 (58%)
1 or more	374 (42%)	374 (42%)
HTN or AF	620 (74%)	620 (74%)
Census Tract Poverty Level<10% ^b	511 (58%)	--
Cancer Stage ^c		
0	58 (7%)	--
1	247 (28%)	--
2	330 (37%)	--
3	119 (14%)	--
4	61 (7%)	--
Unknown	66 (7%)	--

Abbreviations: SD, standard deviation; HTN, hypertension; AF, atrial fibrillation

^aSEER registries were categorized into geographic regions for matching as follows: South (Louisiana, Kentucky, Georgia), Northeast (Connecticut, New Jersey), Midwest (Utah, New Mexico, Iowa, Detroit), and West (Hawaii, California, and Seattle, Washington).

^bNumber and proportion of patients who live in areas where less than 10% of people are below the poverty line according to the 2000 census.

^cRefers to the American Joint Committee on Cancer (AJCC) staging schema. Cancers from 2002 through 2003 were staged according to the AJCC third edition definitions, while cancers diagnosed from 2004 through 2011 were staged according to the sixth edition.

Table 2

Cumulative incidence of arterial thromboembolism and associated relative hazards for male breast cancer patients compared to controls.

Group	3 months			6 month			1 year			2 years			3 years		
	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)
Cases	3.4 (2.2–4.6)	1.8 (1.0–3.2)	5.7 (4.1–7.2)	1.6 (1.0–2.6)	1.4 (1.0–2.0)	8.3 (6.5–10.1)	13.3 (11.0–15.6)	1.2 (0.9–1.5)	18.6 (16.0–21.3)	11.9 (9.7–14.1)	1.2 (1.0–1.6)	15.3 (12.8–17.7)	15.3 (12.8–17.7)	1.2 (1.0–1.6)	15.3 (12.8–17.7)
Controls	1.9 (1.0–2.8)		3.5 (2.3–4.7)			6.0 (4.4–7.6)									

Abbreviations: Cum. Inc., Cumulative Incidence; CI, Confidence Interval; HR, Hazard Ratio.

Table 3
Cumulative incidence of myocardial infarction and associated relative hazards for male breast cancer patients compared to controls.

Group	3 months		6 month		1 year		2 years		3 years	
	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)
Cases	1.8 (0.9– 2.7)	1.8 (0.8– 4.0)	2.5 (1.5– 3.5)	1.8 (0.9– 3.7)	3.3 (2.1– 4.5)	1.1 (0.7– 1.9)	5.6 (4.0– 7.1)	0.9 (0.6– 1.3)	7.7 (5.9– 9.5)	1.0 (0.7– 1.4)
Controls	1.0 (0.4– 1.7)		1.4 (0.6– 2.1)		3.0 (1.8– 4.1)		6.4 (4.8– 8.1)		7.6 (5.8– 9.5)	

Abbreviations: Cum. Inc., Cumulative Incidence; CI, Confidence Interval; HR, Hazard Ratio.

Table 4

Cumulative incidence of ischemic stroke and associated relative hazards for male breast cancer patients compared to controls.

Group	3 months		6 month		1 year		2 years		3 years	
	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)	Cum. Inc. (95% CI)	HR (95% CI)
Cases	1.6 (0.8–2.4)	1.4 (0.6–3.2)	3.2 (2.0–4.3)	1.3 (0.8–2.4)	5.4 (3.9–6.9)	1.5 (0.9–2.3)	9.4 (7.4–11.3)	1.3 (1.0–1.9)	13.9 (11.5–16.3)	1.5 (1.1–1.9)
Controls	1.1 (0.4–1.8)		2.4 (1.4–3.4)		3.7 (2.5–5.0)		7.1 (5.4–8.8)		9.8 (7.8–11.8)	

Abbreviations: Cum. Inc., Cumulative Incidence; CI, Confidence Interval; HR, Hazard Ratio.