original article

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Risk factors and incidence of thromboembolic events (TEEs) in older men and women with breast cancer

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Background: The purpose of this study is to evaluate the risk factors and the prevalence of thromboembolic events (TEEs) in breast cancer patients.

Patients and methods: This is a retrospective cohort study using the Surveillance, Epidemiology, and End Results-Medicare database. Breast cancer patients diagnosed from 1992 to 2005 ≥66 years old were identified. International Classification of Diseases, Ninth Revision, and Healthcare Common Procedure Coding System codes were used to identify TEEs within 1 year of the breast cancer diagnosis. Analyses were conducted using descriptive statistics and logistic regression.

Results: A total of 89 841 patients were included, of them 2658 (2.96%) developed a TEE. In the multivariable analysis, males had higher risk of a TEE than women [odd ratio (OR) = 1.57; confidence interval (CI) 1.10–2.25] and blacks had higher risk than whites (OR = 1.20; CI 1.04–1.40). Compared with stage I patients, patients with stage II, III and IV had 22%, 39% and 98% increase, respectively, in risk. Placement of central catheters (OR = 2.71; CI 2.43–3.02), chemotherapy treatment (OR = 1.66; CI 1.48–1.86) or treatment with erythropoiesis-stimulating agents (ESAs) (OR = 1.33; CI 1.33–1.52) increase the risk. Other significant predictors included comorbidities, age, receptor status, marital status and year of diagnosis. Similar estimates were seen for pulmonary embolism, deep vein thromboembolism and other TEEs.

Conclusions: In total, 2.96% of patients in this cohort developed a TEE within 1 year from breast cancer diagnosis. Stage, gender, race, use of chemotherapy and ESAs, comorbidities, receptor status and catheter placement were associated with the development of TEEs.

Key words: breast cancer, cancer-associated thrombosis, deep venous thrombosis, population-based study, thromboembolic events, thrombosis

introduction

Thromboembolic events (TEEs) are a common complication and a life-threatening condition in cancer patients [1, 2]. Trousseau [3] described in 1868 the relationship between malignancy and venous thrombosis. Today, it is well recognized that thrombosis and cancer are linked by multiple pathophysiological mechanisms and that tumor biology and coagulation processes are integrally connected [4].

Population-based studies have showed that the presence of cancer increases the risk of TEEs by four- and sevenfold [2, 5]. Furthermore, advanced age, race, stage, comorbidities and the use of systemic therapies and intravascular catheters are factors that have been associated with an increased risk of TEE in patients with cancer [1, 5–11]. Different risk estimates have been observed among different primary cancer sites; for example gastric, pancreatic, kidney cancers and astrocytomas are associated with a higher risk of developing a TEE than other cancers [1, 6].

Breast cancer patients are considered to be at relatively low risk of developing a TEE; a recent study reported an incidence rate of 1.2% within 2 years of diagnosis [12]. Data from clinical trials suggest that the risk is higher in patients receiving chemotherapy (2.1%) [13] or in those with metastatic disease (4.4%) [14]. Breast cancer is the most common cancer in women in the United States[15]; therefore, the occurrence of a TEE represents a common clinical problem in patients with breast cancer. In this retrospective study, we sought to explore the incidence and the risk factors associated with TEEs in a large cohort of older patients with newly diagnosed breast cancer.

patients and methods

data source

We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The SEER program, supported by the USA National Cancer Institute (NCI), collects data from tumor registries; during the years included in this study, the database covered 14%–25% of the USA population. The Medicare program is administered by the Centers for Medicare and Medicaid Services and covers 97% of the USA population aged ≥65 years [16]. Of SEER participants who were diagnosed

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with cancer at age ≥65 years, 94% are matched with their Medicare enrollment records [16].

Patient demographics, tumor characteristics, and treatment information were extracted from the SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF); Medicare claims files for durable medical equipment (DME), physician/supplier [National Claims History (NCH)], inpatient service [Medicare Provider Analysis and Review (MEDPAR)], and outpatient service files.

study population

This study included patients ≥66 years old with a diagnosis of stage I–IV breast cancer (American Joint Committee on Cancer Staging third edition). Patients were required to have Medicare Part A and B and not to be members of a Health Maintenance Organization (HMO) for 1 year prior and after their breast cancer diagnosis, because Medicare claims are not complete for HMO members. From the initial 319 395 patients with breast cancer diagnosed from 1992 to 2005, 32 256 had history of prior or subsequent malignancies; 1 089 had an unknown month of diagnosis; 103 599 were <66 years old; 37 389 were unstaged or had an unknown initial stage; 45 511 did not have full coverage of Medicare A and B or were members of an HMO, and 193 had non-carcinoma histology. From them, only the 90 153 patients who developed a TEE within the first year of diagnosis and those not developing a TEE were included. Three hundred and twelve patients with an unknown education level were excluded, in order to preserve confidentiality and maintain at least 15 patients per cell in subgroup analyses, per NCI regulations. A total of 89 841 patients were included.

data extraction and definitions

The main outcome of this study was a TEE within the first year of breast cancer diagnosis. TEEs were defined as pulmonary embolism (PE), deep vein thromboembolism (DVT), or other/unclassified TEEs. To identify TEE cases, the study period for each patient was from 1 year before breast cancer diagnosis to 1 year after breast cancer was diagnosed or death (if within 1 year from breast cancer diagnosis). We identified cases of TEEs using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes from the Medicare claims files DME, NCH, MEDPAR, and outpatient service files. Diagnosis code 415.1x was identified as PE; codes 451, 453.1, 453.2, and 453.4 were identified as DVT; and codes 452, 453, 453.0, 453.3, 453.5, 453.6, 453.7, 453.8, and 453.9 were identified as other/unclassified TEEs. In the MEDPAR files, a patient was identified as having a TEE if there was a claim of PE, DVT, or other TEEs as primary diagnosis. In the other three claims files, a patient was classified as having a TEE if the diagnosis appeared in at least two claims with 30 days apart. After we identified the TEE cases, we merged them and chose the earliest date as the TEE diagnosis date.

Demographic and tumor characteristics were obtained from the PEDSF. For the census tract variables of education and poverty level, quartiles were calculated in increasing order. Chemotherapy was identified from Medicare claims; surgery and radiation therapy were identified from the SEER dataset and Medicare claims. Central venous catheter (CVC) placement in the first year after cancer diagnosis was identified from Medicare claims files DME, MEDPAR, NCH, and outpatient service files. Also the use of erythropoiesis-stimulating agents (ESAs) in the same time period was recorded. Using ICD-9-CM diagnosis and procedure codes, the presence of comorbid conditions from 12 to 1 month before the diagnosis of breast cancer was identified in the Medicare inpatient, outpatient and physicians claims data. A comorbidity score was calculated using Klabunde's adaptation of the Charlson comorbidity index from the SAS macro provided by NCI [12,17–19]. The comorbidities included in the score are myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, diabetes (with and without end-organ damage), chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, renal disease, hemiplegia, and acquired immunodeficiency syndrome.

statistical analysis

Descriptive statistics was used. Chi-square tests were used to compare the frequency of demographic and tumor characteristics between patients who experienced at least one TEE and those who did not. Logistic regression was used to identify risk factors associated with the development of TEE within 1 year of breast cancer diagnosis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The variables entered in the multivariable logistic regression model included age, gender, race, marital status, education level, poverty level, geographical location, year of diagnosis, stage at diagnosis, estrogen receptor (ER) and progesterone receptor (PR) status, comorbidities (Charlson index), surgery, radiation therapy, chemotherapy, presence of a CVC and the use of ESAs. All computer programming and statistical analyses were carried out with the SAS system (SAS Institute Inc., Cary, NC), and all tests were two sided.

results

Our final cohort included 89 841 patients; the median age was 75.8 years. The stage distribution was 52.1%, 34.1%, 7.5% and 6.3% for stages I–IV, respectively. Patient characteristics are shown in Table 1. A total of 2658 (2.96%) patients developed at least one TEE within the first year of breast cancer diagnosis. Among the total study samples, 773 (0.86%) had a PE; 1259 (1.4%) had a DVT; and 1829 (2.04%) had other/unclassified TEEs. Some patients had more than one event; the total number of observed events was 3861. Among the patients who experienced an event, 1646 (62%) had only one type, 821 (31%) had two types, and 191 (7%) had three types of TEE. The majority of the events occurred during the first 3 months after breast cancer diagnosis (39.5%). A total of 26.5% of the events were diagnosed between the third and the sixth month and 34% of the events were seen from months 6 to 12 after diagnosis (Figure 1).

We observed that men with breast cancer were more likely to develop a TEE than women (5.08% versus 2.94%). Black patients had TEEs more frequently than whites or other races (4.96% versus 2.89% versus 2.01%, respectively). Stage had a clear association with the development of TEE with higher rates seen in more advanced stages (1.87% for stage I, 3.3% for stage II, 5.02% for stage III and 7.63% for stage IV). Increased comorbidities as well as the use of chemotherapy (6.09%), CVC placement (9.23%) and the use of ESAs (7.7%) were all associated with a higher event frequency. Similar results were seen when PEs, DVTs and other TEEs were analyzed separately. The frequency of the distribution of risk factors is shown in Table 2.

In the multivariable analysis, we observed that men had an increased risk of developing a TEE compared with women (OR 1.57, 95% CI 1.10–2.25); blacks had higher risk (OR 1.20; 95% CI 1.04–1.40), and other races had reduced risk (OR 0.75; 95% CI 0.62–0.90) when compared with whites. More advanced stages were associated with higher risk; using stage I as a reference, patients with stage II, III and IV breast cancer had 22%, 39% and 98% increased risk, respectively. Patients that did not undergo any breast surgery (OR 1.60, 95% CI 1.34–1.91), and those who had CVC placed (OR 2.71, 95%

Table 1. Characteristics of the study cohort

	Frequency	%
Age (years)		
66–70	22 289	24.81
71–75	22 989	25.59
76–80	20 630	22.96
>80	23 933	26.64
Gender		
Female	89 172	99.26
Male	669	0.74
Race		
White	77 776	86.57
Black	5646	6.28
Other	6419	7.14
Year of diagnosis		
1992	4756	5.29
1993	4439	4.94
1994	4283	4.77
1995	4359	4.85
1996	4306	4.79
1997	4371	4.87
1998	4308	4.80
1999	4452	4.96
2000	8833	9.83
2001	9186	10.22
2002	9236	10.28
2003	9211	10.25
2004	9036	10.06
2005	9065	10.09
Stage		
I	46 831	52.13
II	30 652	34.12
III	6710	7.47
IV	5648	6.29
Estrogen receptor		
Positive	61 660	68.63
Negative	12 108	13.48
Unknown	16 073	17.89
Charlson comorbidity score		
0	69 349	77.19
1	14 516	16.16
2+	5976	6.65
Surgery		
Breast conserving	42 518	47.33
Mastectomy	42 773	47.61
No surgery/unknown	4550	5.06
Radiation therapy		
No	45 405	50.54
Yes	43 123	48.0
Unknown	1313	1.46
Chemotherapy		
No	71 279	79.34
Yes	18 562	20.66
CVC placement		
No	80 425	89.52
Yes	9416	10.48
ESAs use		
No	83 596	93.05
Yes	6245	6.95

CVC, central venous catheter; ESA, erythropoiesis-stimulating agent.

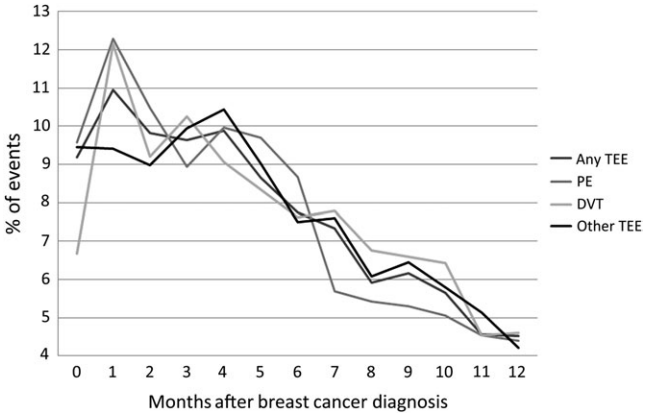

Figure 1. Time of TEE after breast cancer diagnosis. TEE, thromboembolic event; PE, pulmonary embolism; DVT, deep vein thromboembolism.

CI 2.43–3.02), received chemotherapy (OR 1.66, 95% CI 1.48–1.86) or ESAs (OR 1.33, 95% CI 1.17–1.52), had increased risk for developing a TEE. Patients who had ER-negative tumors were less likely to have a TEE (OR 0.84, 95% CI 0.73–0.96). When the analysis was carried out according to the different TEE categories, the observed estimates were similar; however, some of the associations did not achieve statistical significance. The multivariable analyses are shown in Table 3.

discussion

Our study shows that among patients ≥66 years old with breast cancer, the incidence of TEE is 2.96% in the first year of diagnosis. We observed that the incidence is even higher among males and black patients; those with stage IV disease, CVC placement and those receiving chemotherapy and ESAs were at even higher risk. The magnitude of the observed risk was notable. In a multivariable analysis, patients with stage II, III and IV disease had 22%, 39% and 98% increase in risk. The risk among males and black patients was increased 57% and 20%, respectively. The associations with different treatment modalities were also significant; the use of chemotherapy increased the risk by 66%, ESAs increased it by 33% and the use of CVC increased the risk by 170%.

The observed incidence of TEEs is higher than that previously reported. In a large population-based study, Chew et al. [12] observed that among 108 255 patients with breast cancer, the 2-year cumulative risk of a TEE was 1.2%. These results are similar to those observed in clinical trials of patients receiving adjuvant hormonal therapy (1.3%) [20]. The reported incidence of TEE in breast cancer patients receiving adjuvant chemotherapy is 2.1% [13], and for patients with metastatic disease it is 4.4% [14]. This contrasts with our observed TEE incidence of 6.09% in patients receiving chemotherapy and 7.63% in those with metastatic disease. Different studies use different definitions for TEEs, and inter-study comparisons are difficult. Also, it is important to note that our patient population included exclusively patients aged ≥66 years, representing a high-risk cohort, therefore they are not comparable with younger and healthier patients included in clinical trials.

Table 2. Distribution of demographic characteristics and risk factors according to TEE

	Any TEE				PE				DVT				Other TEEs			
	N = 89 841	Cases = 2658			*N* = 87 956	Cases = 773			*N* = 88 442	Cases = 1259			*N* = 89 012	Case = 1829		
	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*
Age (years)																
66–70	22 289	676	3.03	0.172	21 802	189	0.87	0.659	21 950	337	1.54	0.081	22 073	460	2.08	0.119
71–75	22 989	715	3.11		22 482	208	0.93		22 616	342	1.51		22 776	502	2.2	
76–80	20 630	601	2.91		20 212	183	0.91		20 304	275	1.35		20 448	419	2.05	
>80	23 933	666	2.78		23 460	193	0.82		23 572	305	1.29		23 715	448	1.89	
Gender																
Female	89 172	2624	2.94	0.001	87 308	760	0.87	0.002	87 791	1243	1.42	0.025	88 359	1811	2.05	0.205
Male	669	34	5.08		648	13	2.01		651	16	2.46		653	18	2.76	
Race																
White	77 776	2249	2.89	<0.0001	76 193	666	0.87	<0.0001	76 600	1073	1.4	<0.0001	77 071	1544	2	<0.0001
Black	5646	280	4.96		5444	78	1.43		5491	125	2.28		5567	201	3.61	
Other	6419	129	2.01		6319	29	0.46		6351	61	0.96		6374	84	1.32	
Year of diagnosis																
1992	4756	127	2.67	0.346	4661	32	0.69	0.441	4681	52	1.11	0.002	4724	95	2.01	<0.0001
1993	4439	117	2.64		4354	32	0.73		4381	59	1.35		4402	80	1.82	
1994	4283	113	2.64		4202	32	0.76		4231	61	1.44		4244	74	1.74	
1995	4359	125	2.87		4272	38	0.89		4298	64	1.49		4325	91	2.1	
1996	4306	127	2.95		4207	28	0.67		4245	66	1.55		4268	89	2.09	
1997	4371	119	2.72		4289	37	0.86		4314	62	1.44		4335	83	1.91	
1998	4308	135	3.13		4211	38	0.9		4238	65	1.53		4274	101	2.36	
1999	4452	135	3.03		4361	44	1.01		4378	61	1.39		4407	90	2.04	
2000	8833	298	3.37		8602	67	0.78		8666	131	1.51		8765	230	2.62	
2001	9186	295	3.21		8968	77	0.86		9026	135	1.5		9112	221	2.43	
2002	9236	267	2.89		9057	88	0.97		9060	91	1		9178	209	2.28	
2003	9211	274	2.97		9034	97	1.07		9048	111	1.23		9134	197	2.16	
2004	9036	272	3.01		8843	79	0.89		8897	133	1.49		8925	161	1.8	
2005	9065	254	2.8		8895	84	0.94		8979	168	1.87		8919	108	1.21	
Stage																
I	46 831	878	1.87	<0.0001	46 237	284	0.61	<0.0001	46 405	452	0.97	<0.0001	46 545	592	1.27	<0.0001
II	30 652	1012	3.3		29 918	278	0.93		30 158	518	1.72		30 327	687	2.27	
III	6710	337	5.02		6470	97	1.5		6512	139	2.13		6609	236	3.57	
IV	5648	431	7.63		5331	114	2.14		5367	150	2.79		5531	314	5.68	
Estrogen receptor																
Positive	61 660	1717	2.78	<0.0001	60 445	502	0.83	0.007	60 796	853	1.4		61 138	1195	1.95	0.008
Negative	12 108	421	3.48		11 820	133	1.13		11 870	183	1.54	0.503	11 961	274	2.29	
Unknown	16 073	520	3.24		15 691	138	0.88		15 776	223	1.41		15 913	360	2.26	
Charlson comorbidity																
0	69 349	1992	2.87	<0.0001	67 931	574	0.84	0.120	68 294	937	1.37	0.001	68 738	1381	2.01	0.008
1	14 516	435	3		14 219	138	0.97		14 286	205	1.43		14 375	294	2.05	
2+	5976	231	3.87		5806	61	1.05		5862	117	2		5899	154	2.61	
Surgery																
Breast conserving	42 518	999	2.35		41 842	323	0.77	<0.0001	42 016	497	1.18	<0.0001	42 217	698	1.65	<0.0001
Mastectomy	42 773	1331	3.11		41 797	355	0.85		42 092	650	1.54		42 345	903	2.13	
No/unknown	4550	328	7.21		4317	95	2.2		4334	112	2.58		4450	228	5.12	
Radiotherapy																
No	45 405	1307	2.88	0.067	44 438	340	0.77	0.001	44 718	620	1.39	0.523	44 971	873	1.94	0.016
Unknown	1313	51	3.88		1277	15	1.17		1278	16	1.25		1298	36	2.77	
Yes	43 123	1300	3.01		42 241	418	0.99		42 446	623	1.47		42 743	920	2.15	
Chemotherapy																
No	71 279	1527	2.14	<0.0001	70 208	456	0.65	<0.0001	70 495	743	1.05	<0.0001	70 781	1029	1.45	<0.0001
Yes	18 562	1131	6.09		17 748	317	1.79		17 947	516	2.88		18 231	800	4.39	
CVC																
No	80 425	1789	2.22	<0.0001	79 169	533	0.67	<0.0001	79 537	901	1.13	<0.0001	79 851	1215	1.52	<0.0001
Yes	9416	869	9.23		8787	240	2.73		8905	358	4.02		9161	614	6.7	

Table 2. (*Continued*)

	Any TEE				PE				DVT				Other TEEs			
	N = 89 841	Cases = 2658			*N* = 87 956	Cases = 773			*N* = 88 442	Cases = 1259			*N* = 89 012	Case = 1829		
	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*	Total	No_{cases}	%	*P*
ESAs																
No	83 596	2177	2.6	<0.0001	82 069	650	0.79	<0.0001	82 447	1028	1.25	<0.0001	82 912	1493	1.8	<0.0001
Yes	6245	481	7.7		5887	123	2.09		5995	231	3.85		6100	336	5.51	

TEE, thromboembolic event; PE, pulmonary embolism; DVT, deep vein thromboembolism; $No_{cases,}$ number of cases; CVC, central venous catheter; ESA, erythropoiesis-stimulating agent

The first months after a cancer diagnosis are considered the highest risk period for developing TEEs [6, 12]. Consistent with prior reports, we observed that 39.5% of the events occurred during the first 3 months after diagnosis. Some of the hypotheses to explain this phenomenon include the possibility that cancer cells cause activation of the clotting system via humoral and mechanical effects [2]. Other explanations include that in the early months after the diagnosis of cancer, surgery may take place and the inflammatory response can favor a procoagulant state; surgery is also associated with increased risk of TEEs secondary to immobility. Another possible explanation to this peak in the early months after diagnosis is the beginning of active treatment, in particular chemotherapy; the possible invasive interventions to complete the diagnosis work-up and the direct effect of injury after a CVC placement or infections may also play a role [9, 21–24].

A notable finding of this analysis is the increased risk of TEE in male patients. Observational studies including patients with different types of cancer report similar rates of TEE among males and females [1, 6, 22, 25]. In a large study [8] evaluating risk factors for TEE in 1 015 598 hospitalized cancer patients, gender was a predictor of venous thromboembolism, with females having a 14% increase in risk compared with males. It should be noted that a different pattern was observed in our study. Male breast cancer is a rare disease, and ∼1% of all the breast cancers are diagnosed in men. Breast cancer in males is more likely to express ER and PR, with rates as high as 90% [26]. It is accepted that two major factors involved in the stimulation of ER-positive breast cancers are ER signaling and circulating estrogen [27, 28]. There is evidence that extraglandularly produced estradiol-17β and estrone stimulate breast growth in males [29] and that male patients with breast cancer have significantly higher circulating levels of total and free estradiol than non-cancer males [30]. It is possible that risk factors or hormonal variations associated with male breast cancer are also associated with TEE. A study by Kyrle et al. [31] in non-cancer patients reported that males had a higher incidence of recurrent idiopathic venous thromboembolism than women. Similarly, Christiansen et al. [32] observed that in a young non-cancer cohort, males had higher rates of recurrent TEE compared with women. To the best of our knowledge, our observation has not been studied specifically in patients with breast cancer and represents an interesting finding that needs to be confirmed.

In our study, rates of TEE appear to be higher in black patients compared with whites. This observation has been reported by others [7, 8]. Some have suggested that such differences may be related to the type of cancer [6]. However, in a large cohort of breast cancer patients, black patients had a borderline significant increase of 30% in the risk of TEE compared with whites [12]. Comorbidities are another well-studied risk factor for the development of TEEs. The presence of comorbid conditions influences the development of TEEs in patients with different types of cancer. Our data confirm this supposition and provide evidence that the observed increase in risk is associated with an increased number of comorbidities [6, 7, 12, 22, 33–36]. To evaluate comorbidities, we used Klabunde's adaptation of the Charlson index; this scoring system was developed to incorporate the diagnostic and procedure data contained in Medicare claims, to model the 2-year non-cancer mortality [17]. We observed that patients with a Charlson score of 1 did not have a significant increase in risk; however, those with a score ≥2 had 21% higher probability of developing a TEE.

Different treatment strategies have been associated with TEEs, and patients receiving systemic chemotherapy are considered to be at increased risk [1, 2, 37]. In a retrospective study evaluating patients receiving chemotherapy, the reported TEE rate for breast cancer patients was 6% [38], a number nearly identical to what we observed in our study. The exact pathophysiological mechanisms to explain the observed excess of TEEs in patients receiving chemotherapy are not well elucidated, but prothrombotic alterations in coagulation factors, anticoagulant proteins and endothelial cells have been shown to occur following the administration of cytotoxic agents [39–43]. It has been suggested that a prechemotherapy platelet count ≥350 000 and a hemoglobin level <10 g/dl are risk factors for the development of chemotherapy-associated TEEs [7, 25, 35]. Unfortunately, in the SEER-Medicare dataset, no information is available on patients' hematological parameters, so it was not possible to take these factors into consideration in our analysis.

ESAs have been widely used to increase hemoglobin values and reduce transfusion requirements in cancer patients [44–46]. Reports have raised safety concerns as results suggest that the use of ESAs is associated with TEEs [47–49]. In a recent meta-analysis that included 4610 cancer patients, Bennett et al. [48] reported that patients who received ESAs had a higher risk of TEEs (hazard ratio 1.57; 95% CI 1.31–1.87). Our results are

Table 3. Multivariable analysis[a] of risk factors associated with different TEEs

	TEE (events = 2658), OR (95% CI)	PE (events = 773), OR (95% CI)	DVT (events = 1259), OR (95% CI)	Other/unclassified (events = 1829), OR (95% CI)
Age (years)				
66–70	Reference	Reference	Reference	Reference
71–75	1.14 (1.03–1.28)	1.20 (0.98–1.47)	1.09 (0.94–1.27)	1.18 (1.03–1.34)
76–80	1.19 (1.06–1.33)	1.31 (1.06–1.62)	1.08 (0.91–1.27)	1.22 (1.06–1.40)
>80	1.26 (1.12–1.43)	1.36 (1.09–1.71)	1.15 (0.96–1.37)	1.27 (1.10–1.48)
Gender				
Female	Reference	Reference	Reference	Reference
Male	1.57 (1.10–2.25)	2.27 (1.29–3.99)	1.50 (0.90–2.49)	1.25 (0.77–2.02)
Race				
White	Reference	Reference	Reference	Reference
Black	1.20 (1.04–1.40)	1.23 (0.94–1.60)	1.29 (1.04–1.60)	1.20 (1.01–1.43)
Other	0.75 (0.62–0.90)	0.56 (0.38–0.83)	0.72 (0.55–0.94)	0.73 (0.58–0.92)
Year of diagnosis				
1992	Reference	Reference	Reference	Reference
1993	0.97 (0.75–1.25)	1.03 (0.63–1.69)	1.19 (0.82–1.74)	0.88 (0.65–1.19)
1994	0.95 (0.73–1.23)	1.06 (0.64–1.73)	1.26 (0.87–1.83)	0.83 (0.61–1.14)
1995	1.03 (0.80–1.32)	1.22 (0.76–1.96)	1.29 (0.89–1.87)	1.00 (0.74–1.34)
1996	1.03 (0.80–1.32)	0.87 (0.52–1.45)	1.34 (0.92–1.93)	0.97 (0.72–1.30)
1997	0.91 (0.71–1.18)	1.08 (0.67–1.75)	1.19 (0.82–1.74)	0.84 (0.62–1.14)
1998	1.04 (0.81–1.33)	1.11 (0.69–1.79)	1.25 (0.86–1.81)	1.03 (0.78–1.38)
1999	0.95 (0.74–1.23)	1.18 (0.75–1.88)	1.07 (0.74–1.56)	0.84 (0.63–1.14)
2000	0.90 (0.72–1.12)	0.80 (0.52–1.24)	0.95 (0.68–1.33)	0.90 (0.70–1.17)
2001	0.85 (0.68–1.06)	0.89 (0.58–1.36)	0.91 (0.65–1.27)	0.84 (0.65–1.08)
2002	0.74 (0.59–0.93)	0.98 (0.65–1.50)	0.59 (0.42–0.85)	0.76 (0.58–0.98)
2003	0.75 (0.60–0.94)	1.07 (0.71–1.62)	0.72 (0.51–1.01)	0.71 (0.54–0.92)
2004	0.72 (0.57–0.90)	0.84 (0.55–1.29)	0.84 (0.60–1.18)	0.55 (0.42–0.72)
2005	0.66 (0.53–0.83)	0.88 (0.57–1.35)	1.05 (0.75–1.46)	0.37 (0.27–0.49)
Stage				
I	Reference	Reference	Reference	Reference
II	1.22 (1.10–1.35)	1.08 (0.90–1.30)	1.24 (1.08–1.42)	1.21 (1.07–1.36)
III	1.39 (1.20–1.62)	1.26 (0.96–1.65)	1.13 (0.91–1.41)	1.47 (1.23–1.76)
IV	1.98 (1.68–2.33)	1.55 (1.14–2.10)	1.50 (1.17–1.93)	2.15 (1.78–2.59)
Estrogen receptor				
Positive	**Reference**	**Reference**	**Reference**	**Reference**
Negative	0.84 (0.73–0.96)	0.92 (0.72–1.18)	0.72 (0.59–0.88)	0.77 (0.65–0.92)
Unknown	0.80 (0.61–1.04)	1.18 (0.67–2.06)	0.77 (0.52–1.13)	0.68 (0.50–0.92)
Charlson comorbidity				
0	Reference	Reference	Reference	Reference
1	1.03 (0.92–1.14)	1.13 (0.94–1.37)	1.03 (0.88–1.20)	1.01 (0.89–1.15)
2+	1.21 (1.05–1.40)	1.14 (0.87–1.49)	1.34 (1.10–1.64)	1.17 (0.99–1.40)
Surgery				
Breast conserving	Reference	Reference	Reference	Reference
Mastectomy	1.05 (0.95–1.16)	0.98 (0.81–1.18)	1.09 (0.94–1.27)	1.02 (0.90–1.15)
No surgery/unknown	1.60 (1.34–1.91)	1.88 (1.36–2.60)	1.43 (1.08–1.89)	1.52 (1.23–1.87)
Radiation theorapy				
No	Reference	Reference	Reference	Reference
Unknown	1.15 (0.84–1.57)	1.37 (0.78–2.39)	0.83 (0.49–1.41)	1.13 (0.78–1.63)
Yes	1.07 (0.97–1.17)	1.29 (1.08–1.53)	1.07 (0.93–1.23)	1.12 (1.00–1.26)
Chemotherapy				
No	Reference	Reference	Reference	Reference
Yes	1.66 (1.48–1.86)	1.70 (1.38–2.08)	1.72 (1.47–2.03)	1.71 (1.50–1.96)
CVC placement				
No	Reference	Reference	Reference	Reference
Yes	2.71 (2.43–3.02)	2.71 (2.23–3.30)	2.14 (1.83–2.51)	2.79 (2.46–3.17)

Table 3. (*Continued*)

	TEE (events = 2658), OR (95% CI)	PE (events = 773), OR (95% CI)	DVT (events = 1259), OR (95% CI)	Other/unclassified (events = 1829), OR (95% CI)
ESAs use				
No	Reference	Reference	Reference	Reference
Yes	1.33 (1.17–1.52)	1.08 (0.85–1.37)	1.52 (1.27–1.83)	1.39 (1.19–1.61)

[a]Adjusted for age, gender, race, marital status, education level, poverty level, geographical location, year of diagnosis, stage at diagnosis, estrogen and progesterone receptor status, comorbidities (Charlson index), surgery, radiation therapy, chemotherapy, CVC placement and the use of ESAs.
TEE, thromboembolic event; PE, pulmonary embolism; DVT, deep vein thromboembolism; OR, odds ratio; CI, confidence interval; CVC, central venous catheter; ESAs, erythropoiesis-stimulating agents.

consistent with such a risk estimate; we observed that patients who received ESAs had a 33% increase of developing a TEE and a 52% higher risk of DVT compared with patients that did not receive ESAs.

CVC placement is another intervention that has consistently been associated with an increased risk for TEE [10, 50]; we observed that it conferred a 2.7-fold increase in risk. Some of the factors associated with this phenomenon are venous stasis and endothelial injury. However, recent reports associate number of attempts, left side placement and catheter tip position with an increased risk [9]. Unfortunately, we were not able to include those factors in our analysis. Despite the clear relationship between CVC placement and the development of a TEE, no differences in CVC-related TEE rates have been seen in double-blind placebo-controlled trials in cancer patients randomly assigned to receive enoxaparin [51] for 6 weeks or dalteparin [52] for 16 weeks. Current guidelines do not recommend prophylaxis for cancer patients with a CVC [53] but clinical trials should continue to address this question given the important morbidity associated with CVCs.

Our results raise the question of the use of primary prophylaxis in high-risk patients. Our study describes the risk of TEEs in a high-risk breast cancer patient population, and does not represent a valid scoring system, therefore no treatment recommendations can be made based on our results. However, as the National Comprehensive Cancer Network guidelines suggest, inpatient prophylactic therapy should be administered to all patients with active diagnosis of cancer who do not have a contraindication to such therapy [53]. There is unfortunately no data to support extended prophylaxis for medical oncology patients in the outpatient setting [53]. Different scoring systems are available in which individual risk factors are assigned weighted scores, and they provide support for the use of prophylaxis in cancer patients [54–56]; however, none of those score systems have been validated in cancer patients. Khorana et al. [35] reported on a model in cancer patients receiving chemotherapy; if validated in future studies, this score could help identify patients in whom primary prophylaxis should be recommended. Importantly, randomized clinical trials evaluating this concept are warranted.

To the best of our knowledge, this is the largest study examining the risk factors associated with different TEEs within the first year of diagnosis in breast cancer patients aged ≥66 years. One of the strengths of this study is that it involves a large unselected population-based cohort of patients, likely reflecting real clinical practice. It is important to mention that, for the same reasons, our cohort includes a high-risk population, and it is likely that age and comorbidities contributed to the higher incidence of TEEs seen.

A limitation of our study is that the SEER-Medicare data do not allow for assessment of the extent of the disease, the severity of outcomes, or an analysis that takes into account the use of thromboprophylaxis, the patient's history of prior TEEs and performance status or hematological parameters. It is possible that factors such as a large tumor burden or genetic predisposition may impact TEE incidence, but we were not able to adjust for such factors. An inherent limitation of claims-based research is the possible heterogeneity in the diagnosis methods used to identify events. We used established diagnosis codes to identify TEE cases and do not believe that the possible heterogeneity in the diagnosis methods could have caused a significant change in our estimates. A limitation of our study is that we could not include data on tamoxifen use, a medication with known prothrombotic effects. It is possible that the lower rate of TEE seen in patients with ER-negative tumors is a reflection of the increased risk seen in ER+ patients as a result of tamoxifen treatment. As a way to take this into account, we adjusted for ER status in the multivariable model and also included the year of diagnosis as we suspect that the proportion of patients taking tamoxifen decreased in recent years as the use of aromatase inhibitors has become the standard of care in postmenopausal patients. We also carried out a stratified analysis according to ER status (data not shown) and observed that the magnitude and direction of the estimates remained very similar. The effect of age, race, stage, comorbidities, chemotherapy and ESAs use and CVC placement was similar when patients with ER-positive, ER-negative and ER-unknown tumors were analyzed separately, validating our results. Also, the results of our study may not be applicable to a population of younger, and in general, healthier patients. Additional studies are needed to confirm these findings and assess the risk of different TEEs in younger breast cancer patients.

In summary, our results demonstrate that TEEs are a complication seen in patients with breast cancer. In this cohort of patients, the first 3 months after diagnosis were associated with the highest event incidence. Males, black patients and those with advanced stages or positive hormone receptor status are at increased risk. Other subgroups of

patients at significant risk are those receiving chemotherapy or ESAs and those with CVC placement. TEEs in breast cancer patients represent a substantial clinical problem and much work needs to be done to reduce the burden of TEEs. Better risk assessment tools need to be developed to identify high-risk populations who could benefit from pharmacological prophylactic treatment.

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