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Impact of comorbidity on risk of venous thromboembolism in patients with breast cancer: a Danish population-based cohort study

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ABSTRACT

Objectives: To assess the interaction between comorbidity and breast cancer (BC) on the rate of venous thromboembolism (VTE) beyond what can be explained by the independent effects of BC and comorbidity.

Design: Population-based matched cohort study.

Setting: Denmark.

Participants: Danish patients with BC (n=62 376) diagnosed in 1995–2010 and a comparison cohort of women without BC (n=304 803) from the general population were matched to the patients with BC on year of birth in 5-year intervals and on the specific diseases included in the Charlson Comorbidity Index (CCI) and atrial fibrillation and obesity.

Measures: The rate ratios of VTE per 1000 person-years (PY) were computed by comorbidity levels using the CCI, and interaction contrasts (IC) were calculated as a measure of the excess or deficit VTE rate not explained by the independent effects of BC and comorbidity.

Results: Among patients with BC with a CCI score of 1, the 0–1 year VTE rate was 12/1000 PY, and interaction accounted for 10% of the rate (IC=3.2, 95% CI 0.5 to 5.9). Among patients with BC with CCI $\geq$4, the VTE rate was 17, and interaction accounted for 8% of the rate (IC=1.2, 95% CI −1.8 to 4.2). There was no interaction during 2–5 years of follow-up.

Conclusions: There was only little interaction between BC and the CCI score on the rate of VTE.

BACKGROUND

Venous thromboembolism (VTE), that is, deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and mortality, in particular during hospitalisation.[1] Cancer and VTE are strongly related and VTE can be a marker of occult cancer as well as a serious complication of cancer.[2] Cancer-associated VTE risk is up to seven times higher compared to that of the general population,[3–5] and the rate is mainly increased during the first year following cancer diagnosis.[3 6] Important risk factors include cancer type and cancer stage, but may also be related to treatment including chemotherapy and central venous catheters used for treatment administration.[1 7 8]

Breast cancer (BC) is the most common cancer among women in most of the developed world,[9] and an estimated 20% of patients are burdened with major comorbid conditions at diagnosis.[10] While there is evidence for a link between some diseases, such as stroke, heart failure and osteoporosis, and risk of VTE,[11–14] it is largely unknown how chronic diseases in BC affect the risk of VTE compared to the general population free of BC.

To the best of our knowledge, no studies have compared the risk of VTE among patients with BC to a comparison cohort of women free of BC from the general population and accounted for comorbidity. We computed the interaction contrast (IC) as a measure of interaction between BC and

Strengths and limitations of this study

- The study included all Danish patients with breast cancer diagnosed in 1995–2010 and a comparison cohort of women from the general population free of breast cancer. The study had complete follow-up on all participants from the nationwide Danish Civil Registration System.
- The study was conducted in a government financed healthcare system with equal access for the entire Danish population.
- The validity of the Danish National Registry of Patients as a source of information on comorbidity and venous thromboembolism has varying completeness and validity for different diseases.
- The Charlson Comorbidity Index as a measure of the combined burden of comorbidity does not allow for estimation of disease severity and duration.

comorbidity levels using the Charlson Comorbidity Index (CCI) as a measure of comorbidity.[15] The IC is an estimate of the VTE rate that cannot be explained by the effects of BC or comorbidity acting alone.[16]

METHODS
Design and setting
To compare VTE rates in a cohort of patients with BC with corresponding rates in a cohort of women free of BC, we designed a nationwide cohort study including all patients diagnosed with BC in Denmark between 1995 and 2010 and a comparison cohort of women were selected from the general population. Women in the comparison cohort were matched to each patient with BC on year of birth in 5-year intervals and on the specific diseases included in the CCI, and on history of atrial fibrillation and obesity, as atrial fibrillation is treated with anticoagulation and obesity is a risk factor for VTE.[15 17 18]

The study used administrative and medical registries in Denmark, where the national healthcare system provides tax-supported access to primary care and hospitals for all legal residents.[19] The Civil Registration System (CRS) maintains up-to-date information on vital and civil status for all Danish residents.[20] Since 1968, all residents of Denmark have been assigned a Civil Personal Registration (CPR) number, which facilitates accurate linkage between medical registries. This study made use of such registries to provide information on BC and other hospital diagnoses (see online supplementary appendix).

Ascertainment of the BC and comparison cohorts
The Danish Cancer Registry (DCR) was established in 1943 and records all cancers diagnosed in Denmark.[21 22] We identified all female patients with BC diagnosed between 1995 and 2010 and excluded patients with a VTE diagnosis preceding the index (diagnosis) date. For women in the comparison cohort, the index date was defined as the date of BC diagnosis for the matched case.

From the CRS, we selected up to five women from the general population and matched them without replacement to each patient with BC on age (5-year intervals) and on hospital history of specific comorbidities included in the CCI,[15] and in the presence/absence of atrial fibrillation and obesity. We were unable to find matched comparison women to 428 patients with BC due to high age and many comorbidities, which precluded matching. Women in the comparison cohort could not have previous diagnostic codes for BC or VTE as of the date of BC diagnosis for the corresponding case but were eligible for inclusion in the BC cohort if they developed BC.

Comorbidity
The Danish National Registry of Patients (DNRP) contains information on all non-psychiatric discharge

diagnoses for inpatient hospitalisations since 1977. Information on visits to outpatient specialist and emergency departments was added from 1995. The DNRP records diagnoses and dates of hospital contacts.[23] This registry was used to identify all diagnoses of diseases included in the CCI,[15] as well as atrial fibrillation and obesity for members of the two cohorts (see online supplementary appendix). Atrial fibrillation and obesity were included in the CCI with a weight of one.

Venous thromboembolism
The study outcome was VTE, defined as any inpatient or outpatient discharge diagnosis of PE, DVT or other VTE diagnosed after the index date (see online supplementary appendix), thereby excluding VTE that was only diagnosed at emergency departments due to a low positive predictive value.[24] Owing to the little impact on mortality risk associated with DVT alone, patients coded as having both DVT and PE on their first diagnosis date were classified as patients with PE.

Follow-up
The BC and comparison cohorts were followed from the index date until the first occurrence of VTE, death, emigration or 5 years of follow-up, whichever came first. If a matched comparison cohort member received a BC diagnosis, follow-up was censored and the woman was switched to the BC cohort. The person-time was divided into two survivor cohorts, the first with 1 year of follow-up and the second with 2–5 years of follow-up.

Statistical analysis
First, we computed proportions of women in the BC cohort and the matched comparison cohort within categories of age (0–59, 60–69, 70–79 and ≥80 years), index year (1995–1999, 2000–2004 and 2005–2010), baseline CCI score (0, 1, 2–3, ≥4), individual CCI comorbidities, presence/absence of atrial fibrillation and obesity, and—for the BC cohort—BC stage at diagnosis (local, regional, distant or unknown).

Next, we computed cumulative incidence estimates for VTE, which takes into account the competing risk of death (an event that precludes subsequent VTE occurrence).[25]

We then computed the rate of VTE within the categories described above for the two cohorts and created Cox proportional hazard regression models to compute the HRs as a measure of the VTE rate ratio adjusted for age (continuous) and year of BC diagnosis (1995–1999 vs 2005–2010, 2000–2004 vs 2005–2010) to compute rate ratios for VTE within the strata of comorbidity. As comorbid conditions were matched factors, the matching had to be dissolved in all adjusted analyses and for analyses of the 2–5 year survival cohort. To account for changes in the age distribution at 1 year of follow-up, VTE rates for the 2–5 year survivor cohort were standardised to the age distribution of patients with BC as of their index dates. The proportionality assumption in

Table 1 Characteristics of the breast cancer and the matched comparison cohorts, 1994–2010

	Breast cancer cohort		Comparison cohort	
	Women, N	(%)	Women, N	(%)
Number of patients				
0–1 year of follow-up	62 376		304 803	
2–5 years of follow-up	57 857		296 326	
Age group in years				
0–59	27 013	(43)	134 598	(44)
60–69	17 065	(27)	81 640	(27)
70–79	10 846	(17)	53 000	(17)
≥80	7452	(12)	35 565	(12)
Year of cancer diagnosis/index date*				
1995–1999	16 949	(27)	83 263	(27)
2000–2004	18 894	(30)	92 488	(30)
2005–2010	26 533	(43)	129 052	(42)
Cancer stage				
Local	28 936	(46)	N/A	
Regional	24 210	(39)	N/A	
Distant	3302	(5.3)	N/A	
Unknown	5928	(9.5)	N/A	
Charlson Comorbidity Index score				
0	46 856	(75)	231 713	(76)
1	8037	(13)	38 854	(13)
2–3	6437	(10)	30 419	(10)
≥4	1047	(1.7)	3817	(1.3)
Individual comorbidities in the Charlson Comorbidity Index				
Myocardial infarction	1086	(1.7)	4909	(1.6)
Congestive heart failure	1258	(2.0)	5333	(1.7)
Peripheral vascular disease	1267	(2.0)	5598	(1.8)
Cerebrovascular disease	2919	(4.7)	13 530	(4.4)
Dementia	426	(0.7)	1888	(0.6)
Chronic pulmonary disease	3118	(5.0)	14 446	(4.7)
Connective tissue disease	1471	(2.4)	6766	(2.2)
Ulcer disease	1623	(2.6)	7509	(2.5)
Mild liver disease	402	(0.6)	1764	(0.6)
Diabetes I and II	1751	(2.8)	7837	(2.6)
Hemiplegia	87	(0.1)	365	(0.1)
Moderate to severe renal disease	445	(0.7)	1892	(0.6)
Diabetes with end-organ damage	653	(1.0)	2832	(0.9)
Any tumour†	3221	(5.2)	15 196	(5.0)
Leukaemia	66	(0.1)	273	(0.1)
Lymphoma	189	(0.3)	859	(0.3)
Moderate to severe liver disease	77	(0.1)	311	(0.1)
Metastatic solid tumour	296	(0.5)	1320	(0.4)
AIDS	6	(0)	30	(0)
Other comorbidities				
Atrial fibrillation	567	(0.9)	2453	(0.8)
Obesity	1330	(2.1)	5984	(2.0)
Cases of VTE‡				
0–1 year of follow-up				
DVT	195	(39)	309	(46)
PE	178	(35)	235	(35)
Other VTEs	129	(26)	124	(19)
2–5 years of follow-up				
DVT	333	(26)	1025	(34)
PE	289	(22)	827	(28)
Other VTEs	167	(13)	456	(15)

*Defined as date of breast cancer diagnosis for the breast cancer cohort and date of sampling for the matched cohort.
†Excluding breast cancer.
‡Percentages are calculated based on the number of women with VTE.
DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 2 VTE rates for 0–1 and 2–5 year, IC and VTE rate ratio by CCI score for the breast cancer and matched comparison cohorts

CCI score	Cohort	Number of VTEs	Person-years	Standard rate (95% CI)	IC (95% CI)	VTE rate ratio (95% CI)
0–1 year follow-up						
0	Breast	324	45 342	7.1 (6.4 to 7.9)	Ref	4.8 (4.1 to 5.6)
0	Comparison	346	229 978	1.5 (1.4 to 1.7)		
1	Breast	93	7543	12 (10 to 15)	3.2 (0.5 to 5.9)	3.5 (2.7 to 4.6)
1	Comparison	134	37 966	3.5 (3.0 to 4.2)		
2–3	Breast	70	5936	12 (9.2 to 15)	1.2 (−1.8 to 4.2)	2.4 (1.8 to 3.1)
2–3	Comparison	146	29 201	5.0 (4.2 to 5.8)		
≥4	Breast	15	910	17 (9.2 to 26)	−1.3 (−11 to 7.9)	1.3 (0.7 to 2.4)
≥4	Comparison	42	3455	12 (8.8 to 16)		
2–5 year follow-up						
0	Breast	533	135 618	4.3 (3.9 to 4.6)	Ref	2.2 (2.0 to 2.4)
0	Comparison	1384	747 209	2.1 (2.0 to 2.2)		
1	Breast	136	19 861	6.4 (5.3 to 7.6)	0.9 (−0.4 to 2.1)	1.7 (1.4 to 2.1)
1	Comparison	436	109 138	3.4 (3.0 to 3.7)		
2–3	Breast	100	14 766	6.1 (4.7 to 7.5)	−0.5 (−2.1 to 1.0)	1.2 (1.0 to 1.6)
2–3	Comparison	433	79 310	4.5 (4.0 to 5.0)		
≥4	Breast	20	1834	10 (3.9 to 17)	2.3 (−4.3 to 8.9)	1.5 (0.9 to 2.5)
≥4	Comparison	55	7825	5.8 (4.0 to 7.5)		

CCI, Charlson Comorbidity Index; IC, interaction contrast; VTE, venous thromboembolism.

Cox models was examined with log minus log plots, and both this and the linearity assumption of the effect of age were found to be acceptable. The interaction between BC and comorbidity on the rate of VTE was examined by calculating the IC, which measures the excess or deficit rate of VTE above or below that expected given the baseline VTE rate, the effect of BC on the VTE rate, and the effect of comorbidity on the VTE rate, based on the additivity of effects. It is calculated as the difference between the rate differences (VTE rate in the BC cohort minus the VTE rate in the comparison cohort) in the strata with and without comorbidity.[16] The IC is a measure of the synergistic or antagonistic interaction between two factors that cannot be explained by their individual effects.

Analyses were conducted using SAS V.9.2 (SAS Institute Inc, Cary, North Carolina, USA).

The study was approved by the Danish Data Protection Agency (2011–41-6174).

RESULTS

Descriptive statistics of the cohorts are shown in table 1. The study included 62 376 patients with BC and 304 803 women from the general population matched to the patients with BC diagnosed between 1995 and 2010. The median age in the BC cohort was 62.3 years (IQR 52.8, 72.3), and 62 (IQR 52.6, 72.9) in the comparison cohort. In the BC and comparison cohorts, 75% and 76% of all women had a CCI score of 0 at the index date. During the first year of follow-up, there were 502 (0.8%) and 668 (0.2%) cases of VTE in the BC and the matched comparison cohort, respectively, of which 39%

vs 46% were DVT, 35% were PE in both cohorts, and 26% vs 19% were other VTEs, respectively. By 5 years of follow-up, an additional 789 (1.4%) cases of VTE were diagnosed in the BC cohort and 2308 (0.8%) in the comparison cohort.

Table 2 presents the VTE rates, ICs and adjusted VTE rate ratios for 0–1 and 2–5 years of follow-up in the BC and comparison cohorts. After taking into account death as a competing risk, the BC cohort was at higher risk for all types of VTE within 1 year of follow-up (0.80%, 95% CI 0.74 to 0.88 vs 0.22%, 95% CI 0.20 to 0.24) and at 5 years of follow-up (1.6%, 95% CI 1.50 to 1.73 vs 0.93%, 95% CI 0.90 to 0.97). At 1 year of follow-up, the VTE rate was 8.4 (95% CI 7.7 to 9.2) per 1000 person-years (PY) in the BC cohort and 2.2 (95% CI 2.1 to 2.4) per 1000 PY in the comparison cohort (data not shown). In all strata of CCI scores, the BC cohort had higher rates of VTE compared to the comparison cohort, but the corresponding HRs decreased with increasing CCI score. The HR for VTE was 4.8 (95% CI 4.1 to 5.6) for a CCI score of 0, and 1.3 (95% CI 0.7 to 2.4) for a CCI score of ≥4. During 2–5 years of follow-up, the corresponding HRs were 2.2 (95% CI 2.0 to 2.4) for a CCI score of 0 and 1.5 (95% CI 0.9 to 2.5) for a CCI score of ≥4.

The IC analysis revealed a small amount of interaction between BC and the CCI score, which weakened with increasing CCI score, suggesting that the combined effect of BC and comorbidity mainly impacts the VTE rates in the presence of low comorbidity levels. Interaction accounted for 3.2 (95% CI 0.5 to 5.9) cases of VTE per 1000 PY for a CCI score of 1, 1.2 (95% CI −1.8 to 4.2) cases of VTE for a CCI score of 2–3, and −1.3 (95% CI −11 to 7.9) cases of VTE for a CCI score of ≥4/

1000 PY, representing 27%, 10% and −7.6% of total VTE rates, respectively. During 2–5 years of follow-up, weak interaction was only observed for the CCI score of ≥4 (IC, 2.3, 95% CI −4.3 to 8.9/1000 PY), corresponding to 23% of the total VTE rate.

DISCUSSION

In this nationwide study, the BC cohort had elevated rates of VTE compared to women from the comparison cohort in all categories of comorbidity. However, comparing the BC cohort to the comparison cohort within levels of the CCI score, the VTE rate differences remained nearly constant as the comorbidity level increased, whereas the rate ratios declined with increasing CCI score. We found that there was only a small amount of interaction between BC and the CCI score on the VTE rate, which primarily was observed during the first year after BC diagnosis for patients with a CCI score of 1. This pattern of effects and interactions suggests that comorbidity and BC or its treatment affect the rate of VTE for patients with BC with a CCI score of 1 and in the first year of follow-up. Previous studies have found that BC does not confer a large increased risk of VTE compared to many other cancer types,[3] which may provide one explanation for the relatively small amount of interaction in patients with BC compared to women from the general population.

Interaction contrasts were negative in some analyses, although often imprecisely measured. Negative interaction contrasts suggest that the joint effect of BC and comorbidity is less than expected from their individual effects. In women with multiple comorbidities, and at longer times of follow-up, the independent effects of comorbidity and BC therefore dominate the overall risk of VTE, possibly due to the higher baseline risk of VTE contributed by each of these factors.

In our study, patients with BC had higher VTE rates than the comparison cohort women in all strata of comorbidity, particularly in the first year of follow-up. Such an effect is probably due to a prothrombotic state associated with the cancer and cancer-directed treatments such as surgery, chemotherapy and antihormonal therapies.[14 26 27] Other medications used to treat cancer symptoms and comorbid conditions, such as NSAIDs and glucocorticoids, could elevate VTE risk.[28 29] With increasing CCI score, the rates of VTE in the two cohorts approached each other. This finding may be explained by a potentially greater effect of the cumulative comorbidity burden on the VTE risk, while the effect of BC remains similar within each strata of comorbidity.

Therefore, the presence of comorbidity may be a factor worth considering in future prediction models.

This study was based on a nationwide cohort of patients with BC, and we achieved almost complete follow-up through the CRS, limiting selection bias.

Despite these strengths, there are several study limitations to consider. Data on BC obtained from the DCR are virtually complete.[30] The positive predictive values for the CCI diseases recorded in the DNRP are above 80% compared to the medical record review.[31] However, outpatient data were not registered before 1995, and the impact of any resulting misclassification of comorbidities on estimates of the interaction contrast is unclear.[32] The definition of VTE included both inpatient and outpatient discharge VTE diagnoses, but the accuracy of these diagnoses varies for type of diagnosis and hospital department, with the highest positive predictive value of 75% for inpatient diagnoses.[24] To reduce the number of invalid VTE diagnoses, we only included inpatient and outpatient VTE diagnoses, thereby disregarding VTE only diagnosed at emergency departments, which have poor predictive value.[24] Any bias resulting from the potential rate of misclassification could be affected by a diagnosis of BC and lead to surveillance bias, because patients receive thorough medical care, particularly in the initial years following diagnosis.[33] With increasing CCI score, the VTE rates among patients with BC approach the rates of comparison women, suggesting that the amount of medical surveillance is more similar between the cohorts with increasing morbidity. In addition, intravenous catheters used in connection with cancer surgery or chemotherapy are linked to VTE.[34] Such associations could affect the accuracy of DVT diagnoses. Furthermore, we lacked information on several important factors, for example, cancer treatment, abnormal laboratory findings, other medications and intravenous catheters, which could independently affect VTE risk.

In summary, we found only little interaction between BC and the CCI score on the rate of VTE. While there was little interaction, it does appear that patients and physicians should consider comorbidities when contemplating prophylactic anticoagulation for patients with BC.

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