Impact of comorbidity on risk of venous thromboembolism in breast cancer patients – A Danish population-based cohort study.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5, 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	7, 8
		(*c*) Explain how missing data were addressed	7, 8
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	12, 13
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16, 17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Title: Impact of comorbidity on risk of venous thromboembolism in breast cancer patients – A Danish population-based cohort study

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Running title: Breast cancer, comorbidity and risk of VTE

Key words: Breast neoplasms, comorbidity, morbidity, venous thrombosis, haemostasis, epidemiology

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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 BC patients (n=62,376) diagnosed 1995–2010 and a comparison cohort of women without BC (n=304,803) from the general population matched to the BC patients on year of birth in five-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 (PYs) were computed by comorbidity levels using the CCI, and interaction contrast were calculated as a measure of the excess or deficit VTE rate not explained by the independent effects of BC and comorbidity.

Results: Among BC patients with a CCI score of 1, the 0-1 year VTE rate was 12 per 1000 person-years (PYs), and interaction accounted for 10% of the rate (IC= 3.2, 95% confidence interval (CI), 0.5, 5.9). Among BC patients with CCI ≥4, the VTE rate was 17, and interaction accounted for 8% of the rate (IC= 1.2, 95%CI, -1.8, 4.2). There was no interaction during ≥1-5 years of follow-up.

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

Article summary

- The study included all Danish breast cancer patients diagnosed 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 health care 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 VTE has varying completeness and validity for different diseases.

- The CCI as a measure of the combined burden of comorbidity does not allow for estimation of disease severity and duration.

Background

Venous thromboembolism (VTE), i.e., deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and mortality, in particular during hospitalization.[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 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 breast cancer affect the risk of VTE compared to the general population free of breast cancer.

To our knowledge, no studies have compared the risk of VTE among BC patients to a comparison cohort of women free of BC and accounted for comorbidity. We computed the interaction contrast (IC) as a measure of interaction between breast cancer and 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 breast cancer or comorbidity acting alone.[16]

Methods

Design and setting

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

The study used administrative and medical registries in Denmark, where the national health care 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 breast cancer and other hospital diagnoses (see appendix).[20]

Ascertainment of the breast cancer 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 breast cancer patients 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 breast cancer 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 breast cancer patient on age (5-year intervals) and on hospital history of specific comorbidities included in the CCI,[15] and on presence/absence of atrial fibrillation and obesity. Women in the comparison cohort could not have previous diagnostic codes for breast cancer or VTE as of the date of breast cancer diagnosis for the corresponding case.

Comorbidity

The Danish National Registry of Patients (DNRP) contains information on all non-psychiatric discharge diagnoses for inpatient hospitalizations 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 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 in- or outpatient discharge diagnosis of PE, DVT, or other VTE diagnosed after the index date (see Appendix).[24] Due 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 PE patients.

Follow-up

The breast cancer and comparison cohorts were followed from the index date until the first occurrence of VTE, death, emigration or five years of follow-up, whichever came first. If a matched comparison cohort member received a breast cancer diagnosis, follow-up was censored and the woman was switched to the breast cancer cohort. The person-time was divided into two survivor cohorts, the first with one year of follow-up and the second with more than one to five years of follow-up.

Statistical analysis

First, we computed proportions of women in the breast cancer 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 breast cancer cohort—breast cancer stage at diagnosis (local, regional, distant, or unknown).

Next, the Kaplan-Meier (KM) method was used to compute crude survival and cumulative incidence estimates for VTE accounting for the competing risk of death.[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 hazard ratios (HRs) adjusted for age (continuous) and year of breast cancer diagnosis (1995–1999 vs. 2005–2010, 2000–2004 vs.

2005–2010) to compute rate ratios for VTE within strata of comorbidity. As comorbid conditions were matched factors, the matching had to be dissolved in all adjusted analyses and for analyses of the >1–5 year survival cohort. To account for changes in the age distribution at one year of follow-up, VTE rates for the >1–5 year survivor cohort were standardized to the age distribution of the breast cancer patients as of their index dates.

The interaction between breast cancer 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 breast cancer on the VTE rate, and the effect of comorbidity on the VTE rate.[16] It is calculated as the difference between the rate differences (VTE rate in the breast cancer cohort minus the VTE rate in the comparison cohort) in the strata with and without comorbidity.[16]

Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

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 breast cancer patients and 304,803 women from the general population matched to the breast cancer patients diagnosed between 1995 and 2010. The median age in the breast cancer cohort was 62.3 years (inter-quartile range, 52.8, 72.3), and 75% of the cohort members had a CCI score of 0 at the time of breast cancer diagnosis. During the first year of follow-up, there were 502 and 668 cases of VTE in the breast cancer 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 five years of follow-up, an additional 789 cases of VTE were diagnosed in the breast cancer cohort and 2,308 in the comparison cohort.

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

The IC analysis revealed a small amount of interaction between breast cancer and the CCI score, which weakened with increasing CCI score, suggesting that the combined effect of breast cancer and comorbidity mainly impacts the VTE rates in presence of low comorbidity levels. Interaction accounted for 3.2 (95%CI, 0.5, 5.9) cases of VTE per 1000 PY for a CCI score of 1, 1.2 (95%CI, –1.8, 4.2) cases of VTE for a CCI score of 2–3, and –1.3 (95%CI, –11, 7.9) cases of VTE for a CCI score of ≥4 per 1000 PY, representing 27%, 10%, and –7.6% of total VTE rates, respectively. During >1–5 years of follow-up weak interaction was only observed for a CCI score of ≥4 (IC, 2.3, 95%CI, –4.3, 8.9/1000PY), corresponding to 23% of the total VTE rate.

Discussion

In this nationwide study, the breast cancer cohort had elevated rates of VTE compared to women from the comparison cohort in all categories of comorbidity. However, comparing the breast cancer cohort to the comparison cohort within levels of the CCI score, 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 breast cancer and the CCI score on the VTE rate, which primarily was observed during the first year after breast cancer diagnosis for patients with a CCI score of 1. This pattern of effects and interactions suggests that comorbidity and breast cancer or its treatment effect the rate of VTE for breast cancer patients with a CCI score of 1 and in the first year of follow-up. In women with multiple comorbidities, and at longer times of follow-up, the independent effects of comorbidity, breast cancer, and its treatments dominate the overall risk of VTE, possibly due to the higher baseline risk of VTE contributed by each of these factors.

In our study, breast cancer patients 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 potential greater effect of the cumulative comorbidity burden on the VTE risk, while the effect of breast cancer 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 breast cancer patients, and we achieved complete follow-up through the CRS, limiting selection bias.

Despite these strengths, there are several study limitations to consider. The positive predictive values for the CCI diseases recorded in the DNRP are high compared to 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 are unclear.[32] The definition of VTE included both in- and outpatient discharge VTE diagnoses. However, the accuracy of these diagnoses vary for type of diagnosis and hospital department, with the highest PPV of 75% for inpatient diagnoses.[24] Any bias resulting from the potential rate of misclassification could be affected by a diagnosis of breast cancer and lead to surveillance bias, because patients receive thorough medical care, particularly in the initial years following diagnosis.[33] 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 use of hormone replacement therapy, other medications, and intravenous catheters, which could independently affect VTE risk.

In summary, we found only little interaction between breast cancer 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 breast cancer patients.

Table 1. Characteristics of the breast cancer and comparison cohorts.				
	Breast cancer cohort		Matched comparison cohort	
	Women, N	(%)	Women, N	(%)
Number of patients				
0–1 year of follow–up	62,376		304,803	
>1–5 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	7,452	(12)	35,565	(12)
Year of cancer diagnosis/index date[a]				
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	3,302	(5.3)	N/A	
Unknown	5,928	(9.5)	N/A	
Charlson Comorbidity Index score				
0	46,856	(75)	231,713	(76)
1	8,037	(13)	38,854	(13)
2–3	6,437	(10)	30,419	(10)
≥4	1,047	(1.7)	3,817	(1.3)
Individual comorbidities in the Charlson Comorbidity Index				
Myocardial infarction	1,086	(1.7)	4,909	(1.6)
Congestive heart failure	1,258	(2.0)	5,333	(1.7)
Peripheral vascular disease	1,267	(2.0)	5,598	(1.8)
Cerebrovascular disease	2,919	(4.7)	13,530	(4.4)
Dementia	426	(0.7)	1,888	(0.6)
Chronic pulmonary disease	3,118	(5.0)	14,446	(4.7)
Connective tissue disease	1,471	(2.4)	6,766	(2.2)
Ulcer disease	1,623	(2.6)	7,509	(2.5)
Mild liver disease	402	(0.6)	1,764	(0.6)
Diabetes I and II	1,751	(2.8)	7,837	(2.6)
Hemiplegia	87	(0.1)	365	(0.1)
Moderate to severe renal disease	445	(0.7)	1,892	(0.6)
Diabetes with end-organ damage	653	(1.0)	2,832	(0.9)
Any tumor[b]	3,221	(5.2)	15,196	(5.0)

Leukemia	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 tumor	296	(0.5)	1,320	(0.4)
AIDS	6	(0)	30	(0)
Other comorbidities				
Atrial fibrillation	567	(0.9)	2,453	(0.8)
Obesity	1,330	(2.1)	5,984	(2.0)
Cases of VTE[c]				
0–1 year of follow–up				
DVT	195	(39)	309	(46)
PE	178	(35)	235	(35)
Other VTEs	129	(26)	124	(19)
>1–5 years of follow–up				
DVT	333	(26)	1,025	(34)
PE	289	(22)	827	(28)
Other VTEs	167	(13)	456	(15)

[a]Defined as date of breast cancer diagnosis for the breast cancer cohort and date of sampling for the matched cohort.
[b]Excluding breast cancer.
[c]Percentages are calculated based on the number of women with VTE.

Table 2. 0–1 year and >1–5 year VTE rate, interaction contrasts (IC), and VTE rate ratio by Charlson Comorbidity Index (CCI) score for the breast cancer and matched comparison cohorts.

0–1 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Rate (95% CI)	IC (95% CI)	HR (95% CI)
0	Breast	324	45,342	7.1 (6.4, 7.9)	Ref	4.8 (4.1, 5.6)
0	Comparison	346	229,978	1.5 (1.4, 1.7)		
1	Breast	93	7,543	12 (10, 15)	3.2 (0.5, 5.9)	3.5 (2.7, 4.6)
1	Comparison	134	37,966	3.5 (3.0, 4.2)		
2–3	Breast	70	5,936	12 (9.2, 15)	1.2 (-1.8, 4.2)	2.4 (1.8, 3.1)
2–3	Comparison	146	29,201	5.0 (4.2, 5.8)		
≥4	Breast	15	910	17 (9.2, 26)	-1.3 (-11, 7.9)	1.3 (0.7, 2.4)
≥4	Comparison	42	3,455	12 (8.8, 16)		

>1–5 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Std. Rate (95%CI)	IC (95%CI)	HR (95% CI)
0	Breast	533	135,618	4.3 (3.9, 4.6)	Ref	2.2 (2.0, 2.4)
0	Comparison	1384	747,209	2.1 (2.0, 2.2)		
1	Breast	136	19,861	6.4 (5.3, 7.6)	0.9 (-0.4, 2.1)	1.7 (1.4, 2.1)
1	Comparison	436	109,138	3.4 (3.0, 3.7)		
2–3	Breast	100	14,766	6.1 (4.7, 7.5)	-0.5 (-2.1, 1.0)	1.2 (1.0, 1.6)
2–3	Comparison	433	79,310	4.5 (4.0, 5.0)		
≥4	Breast	20	1,834	10 (3.9, 17)	2.3 (-4.3, 8.9)	1.5 (0.9, 2.5)
≥4	Comparison	55	7,825	5.8 (4.0, 7.5)		

Appendix. ICD-codes identifying breast cancer, VTE, and comorbidities.		
ICD codes	**ICD-8**	**ICD-10**
Breast cancer	174	C50
Pulmonary embolism	45099	I26
Deep venous thrombosis	45100	I801, I802, I803
Other VTEs	45101, 45108, 45109, 45190, 45191, 45192, 45199, 45299, 453	I800, I808, I809, I81, I82
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09,M30,M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes type1 Diabetes type2	249.00,249.06, 249.07, 249.09 250.00,250.06, 250.07, 250.09	E10.0, E10.1, E10.9 E11.0, E11.1, E11.9
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61

Diabetes with end organ damage Type1 Type2	 249.01-249.05, 249.08 250.01-250.05, 250.08	 E10.2-E10.8 E11.2-E11.8
Any tumor, except breast cancer	140-194, except 174	C00-C75, except C50
Leukemia	204-207	C91-C95
Lymphoma	200-203,275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-198, 199	C76-C80
AIDS	079.83	B21-B24
Atrial fibrillation	42793	I489B
Obesity	27799	E66

Author contributions

AGO, HTS, and TLL conceived and designed the study. AGO, EHP, HTS, TLL acquired, analyzed, and interpreted the data. AGO wrote the first draft and EHP, JPG, PWN, HTS, MV and TLL reviewed, revised, and approved the manuscript.

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Conflict of Interest

The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. The authors declare no conflict of interest.

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Title: Impact of comorbidity on risk of venous thromboembolism in breast cancer patients – 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 BC patients (n=62,376) diagnosed 1995–2010 and a comparison cohort of women without BC (n=304,803) from the general population matched to the BC patients on year of birth in five-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 (PYs) 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 BC patients with a CCI score of 1, the 0-1 year VTE rate was 12 per 1000 person-years (PYs), and interaction accounted for 10% of the rate (IC= 3.2, 95% confidence interval (CI), 0.5, 5.9). Among BC patients with CCI ≥4, the VTE rate was 17, and interaction accounted for 8% of the rate (IC= 1.2, 95%CI, -1.8, 4.2). There was no interaction during 2-5 years of follow-up.

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

Article summary

- The study included all Danish breast cancer patients diagnosed 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 health care 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 VTE has varying completeness and validity for different diseases.

- The CCI as a measure of the combined burden of comorbidity does not allow for estimation of disease severity and duration.

Background

Venous thromboembolism (VTE), i.e., deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and mortality, in particular during hospitalization.[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 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 breast cancer affect the risk of VTE compared to the general population free of breast cancer.

To our knowledge, no studies have compared the risk of VTE among BC patients 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 breast cancer and 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 breast cancer or comorbidity acting alone.[16]

Methods

Design and setting

To compare VTE rates in a cohort of breast cancer patients with corresponding rates in a cohort of women free of breast cancer, we designed a nationwide cohort study including all patients diagnosed with breast cancer in Denmark between 1995 and 2010 and a comparison cohort of women selected from the general population. Women in the comparison cohort were matched to each breast cancer patient on year of birth in five-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 health care 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 breast cancer and other hospital diagnoses (see appendix).

Ascertainment of the breast cancer 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 breast cancer patients 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 breast cancer 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 breast cancer patient on age (5-year intervals) and on hospital history of specific comorbidities included in the CCI,[15] and on presence/absence of atrial fibrillation and obesity. We were unable to find matched comparison women to 428 breast cancer patients due to high age and many comorbidities, which precluded matching. Women in the comparison cohort could not have previous diagnostic codes for breast cancer or VTE as of the date of breast cancer diagnosis for the corresponding case but were eligible for inclusion in the breast cancer cohort if they developed breast cancer.

Comorbidity

The Danish National Registry of Patients (DNRP) contains information on all non-psychiatric discharge diagnoses for inpatient hospitalizations 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 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 in- or outpatient discharge diagnosis of PE, DVT, or other

VTE diagnosed after the index date (see Appendix), thereby excluding VTE that was only diagnosed at emergency departments due to a low positive predictive value%.[24] Because of 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 PE patients.

Follow-up

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

Statistical analysis

First, we computed proportions of women in the breast cancer 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 breast cancer cohort—breast cancer 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 hazard ratios (HRs) as a measure of the VTE rate ratio adjusted for age (continuous) and year of breast cancer diagnosis (1995–1999 vs. 2005–2010, 2000–2004 vs. 2005–2010) to compute rate ratios for VTE within 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 one year of follow-up, VTE rates for the 2–5 year survivor cohort were standardized to the age distribution of the breast cancer patients as of their index dates. The proportionality assumption in Cox models were 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 breast cancer 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 breast cancer on the VTE rate, and the effect of comorbidity on the VTE rate, based on additivity of effects. It is calculated as the difference between the rate differences (VTE rate in the breast cancer 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 version 9.2 (SAS Institute Inc., Cary, NC).

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 breast cancer

patients and 304,803 women from the general population matched to the breast cancer patients diagnosed between 1995 and 2010. The median age in the breast cancer cohort was 62.3 years (inter-quartile range (IQR), 52.8, 72.3), and 62.0 (IQR: 52.6, 72.9) in the comparison cohort. In the breast cancer and comparison cohort, 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 breast cancer 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 five years of follow-up, an additional 789 (1.4%) cases of VTE were diagnosed in the breast cancer cohort and 2,308 (0.8%) in the comparison cohort.

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

The IC analysis revealed a small amount of interaction between breast cancer and the CCI score, which weakened with increasing CCI score, suggesting that the combined effect of breast cancer and comorbidity mainly impacts the VTE rates in presence of low comorbidity levels. Interaction accounted for 3.2 (95%CI, 0.5, 5.9) cases of VTE per 1000 PY for a CCI score of 1, 1.2 (95%CI, –1.8, 4.2) cases of VTE for a CCI score of 2–3, and –1.3 (95%CI, –11, 7.9) cases of VTE for a CCI score of ≥4 per 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 a CCI score of ≥4 (IC, 2.3, 95%CI, –4.3, 8.9/1000PY), corresponding to 23% of the total VTE rate.

Discussion

In this nationwide study, the breast cancer cohort had elevated rates of VTE compared to women from the comparison cohort in all categories of comorbidity. However, comparing the breast cancer cohort to the comparison cohort within levels of the CCI score, 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 breast cancer and the CCI score on the VTE rate, which primarily was observed during the first year after breast cancer diagnosis for patients with a CCI score of 1. This pattern of effects and interactions suggests that comorbidity and breast cancer or its treatment effect the rate of VTE for breast cancer patients 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 BC patients 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 breast cancer 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 breast cancer, 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, breast cancer patients 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 potential greater effect of the cumulative comorbidity burden on the VTE risk, while the effect of breast cancer 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 breast cancer patients, 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 breast cancer 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 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 are unclear.[32] The definition of VTE included both in- and outpatient discharge VTE diagnoses, but the accuracy of these diagnoses vary for type of diagnosis and hospital department, with the highest PPV 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 breast cancer 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 the breast cancer patients 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 breast cancer 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 breast cancer patients.

Author contributions

AGO, HTS, and TLL conceived and designed the study. AGO, EHP, HTS, TLL acquired, analyzed, and interpreted the data. AGO wrote the first draft and EHP, JPG, PWN, HTS, MV and TLL reviewed, revised, and approved the manuscript.

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Conflict of Interest

The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. The authors declare no conflict of interest.

Data Sharing Statement

No additional data available

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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	7,452	(12)	35,565	(12)
Year of cancer diagnosis/index date[a]				
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	3,302	(5.3)	N/A	
Unknown	5,928	(9.5)	N/A	
Charlson Comorbidity Index score				
0	46,856	(75)	231,713	(76)
1	8,037	(13)	38,854	(13)
2–3	6,437	(10)	30,419	(10)
≥4	1,047	(1.7)	3,817	(1.3)
Individual comorbidities in the Charlson Comorbidity Index				
Myocardial infarction	1,086	(1.7)	4,909	(1.6)
Congestive heart failure	1,258	(2.0)	5,333	(1.7)
Peripheral vascular disease	1,267	(2.0)	5,598	(1.8)
Cerebrovascular disease	2,919	(4.7)	13,530	(4.4)
Dementia	426	(0.7)	1,888	(0.6)
Chronic pulmonary disease	3,118	(5.0)	14,446	(4.7)
Connective tissue disease	1,471	(2.4)	6,766	(2.2)
Ulcer disease	1,623	(2.6)	7,509	(2.5)
Mild liver disease	402	(0.6)	1,764	(0.6)
Diabetes I and II	1,751	(2.8)	7,837	(2.6)
Hemiplegia	87	(0.1)	365	(0.1)
Moderate to severe renal disease	445	(0.7)	1,892	(0.6)
Diabetes with end-organ damage	653	(1.0)	2,832	(0.9)
Any tumor[b]	3,221	(5.2)	15,196	(5.0)
Leukemia	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 tumor	296	(0.5)	1,320	(0.4)
AIDS	6	(0)	30	(0)
Other comorbidities				
Atrial fibrillation	567	(0.9)	2,453	(0.8)
Obesity	1,330	(2.1)	5,984	(2.0)
Cases of VTE[c]				
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)	1,025	(34)
PE	289	(22)	827	(28)
Other VTEs	167	(13)	456	(15)

[a]Defined as date of breast cancer diagnosis for the breast cancer cohort and date of sampling for the matched cohort.
[b]Excluding breast cancer.
[c]Percentages are calculated based on the number of women with VTE.

Table 2. 0–1 year and 2–5 year VTE rate, interaction contrasts (IC), and VTE rate ratio by Charlson Comorbidity Index (CCI) score for the breast cancer and matched comparison cohorts.

0–1 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Rate (95% CI)	IC (95% CI)	VTE rate ratio (95% CI)
0	**Breast**	324	45,342	7.1 (6.4, 7.9)	Ref	4.8 (4.1, 5.6)
0	**Comparison**	346	229,978	1.5 (1.4, 1.7)		
1	**Breast**	93	7,543	12 (10, 15)	3.2 (0.5, 5.9)	3.5 (2.7, 4.6)
1	**Comparison**	134	37,966	3.5 (3.0, 4.2)		
2–3	**Breast**	70	5,936	12 (9.2, 15)	1.2 (-1.8, 4.2)	2.4 (1.8, 3.1)
2–3	**Comparison**	146	29,201	5.0 (4.2, 5.8)		
≥4	**Breast**	15	910	17 (9.2, 26)	-1.3 (-11, 7.9)	1.3 (0.7, 2.4)
≥4	**Comparison**	42	3,455	12 (8.8, 16)		

2–5 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Std. Rate (95%CI)	IC (95%CI)	VTE rate ratio (95% CI)
0	**Breast**	533	135,618	4.3 (3.9, 4.6)	Ref	2.2 (2.0, 2.4)
0	**Comparison**	1384	747,209	2.1 (2.0, 2.2)		
1	**Breast**	136	19,861	6.4 (5.3, 7.6)	0.9 (-0.4, 2.1)	1.7 (1.4, 2.1)
1	**Comparison**	436	109,138	3.4 (3.0, 3.7)		
2–3	**Breast**	100	14,766	6.1 (4.7, 7.5)	-0.5 (-2.1, 1.0)	1.2 (1.0, 1.6)
2–3	**Comparison**	433	79,310	4.5 (4.0, 5.0)		
≥4	**Breast**	20	1,834	10 (3.9, 17)	2.3 (-4.3, 8.9)	1.5 (0.9, 2.5)
≥4	**Comparison**	55	7,825	5.8 (4.0, 7.5)		

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Title: Impact of comorbidity on risk of venous thromboembolism in breast cancer patients – A Danish population-based cohort study

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Running title: Breast cancer, comorbidity and risk of VTE

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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 BC patients (n=62,376) diagnosed 1995–2010 and a comparison cohort of women without BC (n=304,803) from the general population matched to the BC patients on year of birth in five-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 (PYs) 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 BC patients with a CCI score of 1, the 0-1 year VTE rate was 12 per 1000 person-years (PYs), and interaction accounted for 10% of the rate (IC= 3.2, 95% confidence interval (CI), 0.5, 5.9). Among BC patients with CCI ≥4, the VTE rate was 17, and interaction accounted for 8% of the rate (IC= 1.2, 95%CI, -1.8, 4.2). There was no interaction during 2~~≥1~~-5 years of follow-up.

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

Article summary

- The study included all Danish breast cancer patients diagnosed 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 health care 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 VTE has varying completeness and validity for different diseases.

- The CCI as a measure of the combined burden of comorbidity does not allow for estimation of disease severity and duration.

Background

Venous thromboembolism (VTE), i.e., deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and mortality, in particular during hospitalization.[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 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 breast cancer affect the risk of VTE compared to the general population free of breast cancer.

To our knowledge, no studies have compared the risk of VTE among BC patients 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 breast cancer and 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 breast cancer or comorbidity acting alone.[16]

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Methods

Design and setting

To compare VTE rates in a cohort of breast cancer patients with corresponding rates in a cohort of women free of breast cancer, we designed a nationwide cohort study including all patients diagnosed with breast cancer in Denmark between 1995 and 2010 and a comparison cohort of women selected from the general population. Women in the comparison cohort were matched to each breast cancer patient on year of birth in five-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 health care 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 breast cancer and other hospital diagnoses (see appendix).

Ascertainment of the breast cancer 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 breast cancer patients 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 breast cancer 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 breast cancer patient on age (5-year intervals) and on hospital history of specific comorbidities included in the CCI,[15] and on presence/absence of atrial fibrillation and obesity. We were unable to find matched comparison women to 428 breast cancer patients due to high age and many comorbidities, which precluded matching. Women in the comparison cohort could not have previous diagnostic codes for breast cancer or VTE as of the date of breast cancer diagnosis for the corresponding case but were eligible for inclusion in the breast cancer cohort if they developed breast cancer.

Comorbidity

The Danish National Registry of Patients (DNRP) contains information on all non-psychiatric discharge diagnoses for inpatient hospitalizations 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 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 in- or outpatient discharge diagnosis of PE, DVT, or other

VTE diagnosed after the index date (see Appendix), thereby excluding VTE that was only diagnosed at emergency departments due to a low positive predictive value%.[24] Because of 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 PE patients.

Follow-up

The breast cancer and comparison cohorts were followed from the index date until the first occurrence of VTE, death, emigration or five years of follow-up, whichever came first. If a matched comparison cohort member received a breast cancer diagnosis, follow-up was censored and the woman was switched to the breast cancer cohort. The person-time was divided into two survivor cohorts, the first with one year of follow-up and the second with two~~more than one~~ to five years of follow-up.

Statistical analysis

First, we computed proportions of women in the breast cancer 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 breast cancer cohort—breast cancer 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]

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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 hazard ratios (HRs) as a measure of the VTE rate ratio adjusted for age (continuous) and year of breast cancer diagnosis (1995–1999 vs. 2005–2010, 2000–2004 vs. 2005–2010) to compute rate ratios for VTE within 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~~>1~~–5 year survival cohort. To account for changes in the age distribution at one year of follow-up, VTE rates for the 2~~>1~~–5 year survivor cohort were standardized to the age distribution of the breast cancer patients as of their index dates. The proportionality assumption in Cox models were 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 breast cancer 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 breast cancer on the VTE rate, and the effect of comorbidity on the VTE rate, based on additivity of effects. It is calculated as the difference between the rate differences (VTE rate in the breast cancer 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 version 9.2 (SAS Institute Inc., Cary, NC).

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 breast cancer patients and 304,803 women from the general population matched to the breast cancer patients diagnosed between 1995 and 2010. The median age in the breast cancer cohort was 62.3 years (inter-quartile range (IQR), 52.8, 72.3), and 62.0 (IQR: 52.6, 72.9) in the comparison cohort. ~~and~~ In the breast cancer and comparison cohort, 75% and 76% of all women~~the cohort members~~ had a CCI score of 0 at the index date~~time of breast cancer diagnosis~~. During the first year of follow-up, there were 502 (0.8%) and 668 (0.2%) cases of VTE in the breast cancer 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 five years of follow-up, an additional 789 (1.4%) cases of VTE were diagnosed in the breast cancer cohort and 2,308 (0.8%) in the comparison cohort.

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

(95%CI, 0.9, 2.5) for a CCI score of ≥4.

The IC analysis revealed a small amount of interaction between breast cancer and the CCI score, which weakened with increasing CCI score, suggesting that the combined effect of breast cancer and comorbidity mainly impacts the VTE rates in presence of low comorbidity levels. Interaction accounted for 3.2 (95%CI, 0.5, 5.9) cases of VTE per 1000 PY for a CCI score of 1, 1.2 (95%CI, –1.8, 4.2) cases of VTE for a CCI score of 2–3, and –1.3 (95%CI, –11, 7.9) cases of VTE for a CCI score of ≥4 per 1000 PY, representing 27%, 10%, and –7.6% of total VTE rates, respectively. During 2~~>1~~–5 years of follow-up weak interaction was only observed for a CCI score of ≥4 (IC, 2.3, 95%CI, –4.3, 8.9/1000PY), corresponding to 23% of the total VTE rate.

Discussion

In this nationwide study, the breast cancer cohort had elevated rates of VTE compared to women from the comparison cohort in all categories of comorbidity. However, comparing the breast cancer cohort to the comparison cohort within levels of the CCI score, 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 breast cancer and the CCI score on the VTE rate, which primarily was observed during the first year after breast cancer diagnosis for patients with a CCI score of 1. This pattern of effects and interactions suggests that comorbidity and breast cancer or its treatment effect the rate of VTE for breast cancer patients 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

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the relatively small amount of interaction in BC patients 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 breast cancer 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 breast cancer, therefore, dominate the overall risk of VTE, possibly due to the higher baseline risk of VTE contributed by each of these factors.

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In our study, breast cancer patients 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 potential greater effect of the cumulative comorbidity burden on the VTE risk, while the effect of breast cancer 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 breast cancer patients, 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 breast cancer obtained from the DCR are virtually complete.[30] The positive predictive values for the CCI diseases

recorded in the DNRP are above 80% ~~high~~ compared to 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 are unclear.[32] The definition of VTE included both in- and outpatient discharge VTE diagnoses, but the accuracy of these diagnoses vary for type of diagnosis and hospital department, with the highest PPV 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 breast cancer 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 the breast cancer patients 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~~use of hormone replacement therapy~~, other medications, and intravenous catheters, which could independently affect VTE risk.

In summary, we found only little interaction between breast cancer 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 breast cancer patients.

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

	Breast cancer cohort		~~Matched c~~Comparison cohort	
	Women, N	(%)	Women, N	(%)
Number of patients				
0–1 year of follow–up	62,376		304,803	
2~~>1~~–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	7,452	(12)	35,565	(12)
Year of cancer diagnosis/index date[a]				
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	3,302	(5.3)	N/A	
Unknown	5,928	(9.5)	N/A	
Charlson Comorbidity Index score				
0	46,856	(75)	231,713	(76)
1	8,037	(13)	38,854	(13)
2–3	6,437	(10)	30,419	(10)
≥4	1,047	(1.7)	3,817	(1.3)
Individual comorbidities in the Charlson Comorbidity Index				
Myocardial infarction	1,086	(1.7)	4,909	(1.6)
Congestive heart failure	1,258	(2.0)	5,333	(1.7)
Peripheral vascular disease	1,267	(2.0)	5,598	(1.8)
Cerebrovascular disease	2,919	(4.7)	13,530	(4.4)
Dementia	426	(0.7)	1,888	(0.6)
Chronic pulmonary disease	3,118	(5.0)	14,446	(4.7)
Connective tissue disease	1,471	(2.4)	6,766	(2.2)
Ulcer disease	1,623	(2.6)	7,509	(2.5)
Mild liver disease	402	(0.6)	1,764	(0.6)
Diabetes I and II	1,751	(2.8)	7,837	(2.6)
Hemiplegia	87	(0.1)	365	(0.1)
Moderate to severe renal disease	445	(0.7)	1,892	(0.6)
Diabetes with end-organ damage	653	(1.0)	2,832	(0.9)
Any tumor[b]	3,221	(5.2)	15,196	(5.0)

Leukemia	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 tumor	296	(0.5)	1,320	(0.4)
AIDS	6	(0)	30	(0)
Other comorbidities				
Atrial fibrillation	567	(0.9)	2,453	(0.8)
Obesity	1,330	(2.1)	5,984	(2.0)
Cases of VTE[c]				
0–1 year of follow–up				
DVT	195	(39)	309	(46)
PE	178	(35)	235	(35)
Other VTEs	129	(26)	124	(19)
2~~>1~~–5 years of follow–up				
DVT	333	(26)	1,025	(34)
PE	289	(22)	827	(28)
Other VTEs	167	(13)	456	(15)

[a]Defined as date of breast cancer diagnosis for the breast cancer cohort and date of sampling for the matched cohort.
[b]Excluding breast cancer.
[c]Percentages are calculated based on the number of women with VTE.

Table 2. 0–1 year and 2~~>1~~–5 year VTE rate, interaction contrasts (IC), and VTE rate ratio by Charlson Comorbidity Index (CCI) score for the breast cancer and matched comparison cohorts.

0–1 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Rate (95% CI)	IC (95% CI)	VTE rate ratio~~HR~~ (95% CI)
0	**Breast**	324	45,342	7.1 (6.4, 7.9)	Ref	4.8 (4.1, 5.6)
0	**Comparison**	346	229,978	1.5 (1.4, 1.7)		
1	**Breast**	93	7,543	12 (10, 15)	3.2 (0.5, 5.9)	3.5 (2.7, 4.6)
1	**Comparison**	134	37,966	3.5 (3.0, 4.2)		
2–3	**Breast**	70	5,936	12 (9.2, 15)	1.2 (-1.8, 4.2)	2.4 (1.8, 3.1)
2–3	**Comparison**	146	29,201	5.0 (4.2, 5.8)		
≥4	**Breast**	15	910	17 (9.2, 26)	-1.3 (-11, 7.9)	1.3 (0.7, 2.4)
≥4	**Comparison**	42	3,455	12 (8.8, 16)		

2~~>1~~–5 year follow-up

CCI score	Cohort	Number of VTEs	Person-years	Std. Rate (95%CI)	IC (95%CI)	VTE rate ratio~~HR~~ (95% CI)
0	**Breast**	533	135,618	4.3 (3.9, 4.6)	Ref	2.2 (2.0, 2.4)
0	**Comparison**	1384	747,209	2.1 (2.0, 2.2)		
1	**Breast**	136	19,861	6.4 (5.3, 7.6)	0.9 (-0.4, 2.1)	1.7 (1.4, 2.1)
1	**Comparison**	436	109,138	3.4 (3.0, 3.7)		
2–3	**Breast**	100	14,766	6.1 (4.7, 7.5)	-0.5 (-2.1, 1.0)	1.2 (1.0, 1.6)
2–3	**Comparison**	433	79,310	4.5 (4.0, 5.0)		
≥4	**Breast**	20	1,834	10 (3.9, 17)	2.3 (-4.3, 8.9)	1.5 (0.9, 2.5)
≥4	**Comparison**	55	7,825	5.8 (4.0, 7.5)		

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Appendix. ICD-codes identifying breast cancer, VTE, and comorbidities.

ICD codes	ICD-8	ICD-10
Breast cancer	174	C50
Pulmonary embolism	45099	I26
Deep venous thrombosis	45100	I801, I802, I803
Other VTEs	45101, 45108, 45109, 45190, 45191, 45192, 45199, 45299, 453	I800, I808, I809, I81, I82
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09,M30,M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes type1	249.00,249.06, 249.07, 249.09	E10.0, E10.1, E10.9
Diabetes type2	250.00,250.06, 250.07, 250.09	E11.0, E11.1, E11.9
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with end organ damage Type1	249.01-249.05, 249.08 250.01-250.05, 250.08	E10.2-E10.8

Type2		E11.2-E11.8
Any tumor, except breast cancer	140-194, except 174	C00-C75, except C50
Leukemia	204-207	C91-C95
Lymphoma	200-203,275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-198, 199	C76-C80
AIDS	079.83	B21-B24
Atrial fibrillation	42793	I489B
Obesity	27799	E66

Author contributions

AGO, HTS, and TLL conceived and designed the study. AGO, EHP, HTS, TLL acquired, analyzed, and interpreted the data. AGO wrote the first draft and EHP, JPG, PWN, HTS, MV and TLL reviewed, revised, and approved the manuscript.

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Conflict of Interest

The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from

companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. The authors declare no conflict of interest.

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AIDS	079.83	B21-B24
Atrial fibrillation	42793	I489B
Obesity	27799	E66

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5, 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	7, 8
		(*c*) Explain how missing data were addressed	7, 8
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	12, 13
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16, 17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.