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Time-dependent risk and predictors of venous thromboembolism in breast cancer patients: a population-based cohort study

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Conflicts of interest disclosures

None.

Author contributions

Judith Brand: study design, analysis and interpretation of data, article preparation and review. Elham Hedayati, Jonas Ludvigsson, Keith Humphreys, Nirmala Bhoo-Pathy, Jonas Bergh and Per Hall: study design, interpretation of data, article review and editing. Kamila Czene: study design, acquisition of data, interpretation of data and article preparation and review.

Precis

- Breast cancer patients are at highest VTE risk within the first year of diagnosis, but remain at 2-fold increased risk many years after.
- Temporal associations with patient, tumor and treatment characteristics provide insight into the time-dependent etiology of VTE in breast cancer patients.

Abstract

Background: Venous thromboembolism (VTE) is a serious complication of cancer and its treatment. We assessed the risk and clinical predictors of VTE in breast cancer patients by time since diagnosis.

Methods: A Swedish population-based study including 8338 breast cancer patients diagnosed from 2001-2008 in the Stockholm-Gotland region, with complete follow-up until 2012. Incidence of VTE was compared with that of 39013 age-matched reference individuals from the general population. Cox and flexible parametric models were used to examine associations with patient, tumor and treatment characteristics, accounting for time-dependent effects.

Results: Over a median follow-up of 7.2 years, 426 breast cancer patients experienced a VTE event (cumulative incidence = 5.1%). VTE incidence was 3-fold increased (HR = 3.28; 95% CI = 2.87-3.74) compared to the general population and was highest 6 months after diagnosis (HR = 8.62; 95% CI = 6.56-11.33) with a sustained increase in risk thereafter (HR at 5 years = 2.19; 95% CI = 1.80-2.67). Independent predictors of VTE were older age, being overweight, pre-existing VTE, comorbid disease, tumor size > 40 mm, progesterone receptor (PR) negative status, > 4 affected lymph nodes, and receipt of chemo- and endocrine therapy. The impact of chemotherapy was limited to early-onset VTE, while comorbid and PR negative disease were more strongly associated with late-onset events.

Conclusions: Our study confirms the long-term risk of VTE in breast cancer patients, and identifies a comprehensive set of clinical risk predictors. Temporal associations with patient, tumor and treatment characteristics inform about the time-dependent etiology of VTE.

Key words: breast cancer, epidemiology, venous thromboembolism, predictors, time-dependent risk modeling.

Introduction

Venous thromboembolism (VTE) is a major health problem affecting ~1-2 per 1000 individuals per year [1, 2]. Breast cancer patients are at 3- to 4-fold increased risk of developing VTE compared to women without cancer [3, 4]. Although VTE risk is relatively low in breast cancer patients compared to other cancer populations, long-term consequences in terms of morbidity [5, 6] and quality of life [7] are substantial, especially for non-metastatic patients who have a rather good prognosis. Moreover, as one of the most common cancers, breast cancer contributes to a large number of cancer-related VTE cases and associated healthcare costs [8].

Several studies have examined the incidence of VTE in breast cancer patients [3, 4, 9, 10], all showing an excess risk shortly after diagnosis, but with a potential sustained increase in risk thereafter [4]. The risk of VTE increases with advanced clinical stages [3, 4, 9] and randomized clinical trials (RCTs) have reported higher VTE rates during treatment with chemo- and endocrine therapy [11-13]. Few studies, however, have assessed the independent contribution of tumor, treatment and other patient-related factors to VTE risk and little is known about predictors of early vs. late-onset events. Chemotherapy, for instance, has been suggested to influence short-term risk only [10, 14, 15], while tumor-specific factors associated with locoregional recurrence and distant metastasis [16, 17] may have a larger impact on long-term VTE risk, given the close interrelation between cancer progression and activation of the coagulation system.[18, 19] Identification of time-dependent risk factors is also relevant for the timing of preventive strategies, including early detection and short-term prophylaxis covering periods of highest risk.

In the present study we aimed to assess the risk and predictors of VTE in a population-based breast cancer cohort, by time since diagnosis. We studied the impact of routinely available clinical parameters, which can easily be incorporated into future risk stratification models.

Methods

Breast cancer cohort

Our source population comprised women diagnosed with primary invasive breast cancer between 2001 and 2008 in the Stockholm-Gotland region, as identified through the Stockholm Breast Cancer Register. The register has about 99% completeness and provides detailed information on tumor/treatment characteristics, and routine follow-up on locoregional recurrences and distant metastases [20]. For the present study, we included patients diagnosed at age 25-75 years without distant metastasis at diagnosis (N = 8338). The cohort was linked by the unique personal identity number to the Cancer Register, Patient Register, Cause of Death Register and Total Population Register and follow-up was complete until 31 December 2012. We also performed linkage with the Prescribed Drug Register which contains data on all drugs dispensed from Swedish pharmacies from July 2005 onward. Self-reported information on weight and height [from which body mass index (BMI) was calculated] was available for a subset of 4687 patients who were invited in 2009 to participate in Libro-1, a study aimed at identifying risk and prognostic factors for breast cancer [21]. The study was approved by the Regional Ethical Review Board in Stockholm and all Libro-1 participants gave written informed consent.

Age-matched reference individuals

We assembled a comparison cohort based on the Total Population Register with cross-linkage to the Cancer Register, Patient Register, Cause of Death Register and Prescribed Drug Register as described above. The Total Population Register contains information on area of residence, vital status and dates of immigration and emigration for all Swedish residents. For each patient, we randomly sampled up to 5 women from the general population living in the Stockholm-Gotland region matched on birth year. Each reference individual was alive and free of breast cancer on the date of the matched patient's diagnosis (the index date). In total, 2677 women could not be matched to an index case, resulting in 39013 age-matched reference individuals. The latest cross-linkage of the Total Population Register to the different health registers was performed at 31 December 2010. Hence, follow-up was shorter in

matched cohort (breast cancer cohort and age-matched population cohort) than case-only (breast cancer cohort) analyses.

Venous thromboembolism

VTE events were identified through the Patient Register, which has nationwide coverage since 1987 and includes all inpatient hospitalizations in Sweden [22]. Since 2001, Swedish counties are also obliged to report hospital-based outpatient physician visits. VTE was defined as a diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) according to International Classification of Diseases codes as described previously [23] (**Supplementary Table 1**). The definition of DVT included diagnoses of lower and upper extremity thrombosis, as well as thrombosis in other specified veins including those of the thorax and abdomen.

Clinical characteristics

The following variables were extracted from the Stockholm Breast Cancer Register: tumor size, histological grade, estrogen/progesterone receptor (ER/PR) status, number of affected lymph nodes, type of surgery, radiotherapy, and receipt of chemo/endocrine therapy, all referring to the date of the primary cancer. Tumor and treatment information was essentially complete (< 5% of the patients had missing data), except for ER (7.3% missing) and PR status (8.9% missing). Grade was routinely collected from 2004 onwards and was missing for 39.3% of the patients. VTE events prior to the index date were identified through the Patient Register. Comorbid conditions were also extracted and summarized into the Charlson Comorbidity Index score.[24]

Statistical analyses

We first assessed the risk of VTE in breast cancer patients as compared to age-matched reference individuals in matched cohort analysis. Numbers of person-years at risk were calculated from the breast cancer diagnosis and corresponding index date in the age-matched reference individuals until the date of the first VTE event, death, emigration, or 31 December 2010 whichever came first.

Cumulative incidences were visualized using Kaplan-Meier plots. Because of the time-dependent risk pattern, time-specific hazard ratios were estimated using flexible parametric survival models (FPM) [25] with time since index date as underlying time scale. FPM uses a restricted cubic spline function to model the baseline hazard and is similar to the Cox proportional hazards model in that it provides a hazard ratio (HR) as measure of association. An advantage of FPM is that non-proportional hazards can easily be fitted by adding a spline for the interaction with time.

Next, we studied the impact of patient, tumor and treatment characteristics in case only analysis using Cox proportional hazards models. Person-time was defined as described above starting from the date of diagnosis, but with extended follow-up until 31 December 2012, as this analysis concerned breast cancer patients only. Proportional hazards assumptions were verified using tests for Schoenfeld residuals and in case of non-proportionality, time-dependent effects were modelled using FPM. We conducted three analyses to study the impact of each clinical parameter: 1. a model adjusting for age at diagnosis only; 2. three grouped models, including respectively all patient, tumor and treatment characteristics with additional adjustment for age at diagnosis, and 3. a multivariable model including all variables.

Three sensitivity analyses were performed. First, we repeated the matched cohort analysis using a more refined outcome definition in patients diagnosed after July 2005. To increase specificity, we only included VTE diagnoses followed by a prescription of vitamin K antagonists (ATC = B01AA) or heparins (ATC = B01AB) within 90 days or death within 30 days of the VTE event. A second sensitivity analysis was carried out to evaluate the long-term risk associated with the first primary tumor. For this analysis, person-time was additionally censored at locoregional recurrence, distant metastasis and diagnosis of a new primary breast cancer. Finally, we repeated all analyses in patients without pre-existing VTE.

Results

Descriptive characteristics of the breast cancer and age-matched population cohort are summarized in **Table 1**. Mean age at breast cancer diagnosis was 57.1 years and 426 patients experienced a VTE event during a median follow-up of 7.2 years. Mean age at VTE diagnosis was lower in breast cancer

patients (62.0 years) than in age-matched reference individuals (65.3 years). The 1, 2 and 5-year cumulative incidences of VTE in the breast cancer cohort were 2.0, 2.5 and 4.0%. Corresponding cumulative incidences in the age-matched population cohort were 0.3, 0.5 and 1.1% respectively (**Figure 1**). VTE rates were 7.9 per 1000 person-years for the breast cancer cohort and 2.4 per 1000 person-years in the age-matched reference individuals **(Supplementary Table 2)**.

Overall, breast cancer patients experienced a 3-fold increased risk of VTE compared to the age-matched reference individuals [HR (95% CI) = 3.28; 2.87-3.74]. The relative risk of VTE was highest the first 6 and 12 months after diagnosis [HR (95% CI) = 8.62 (6.56-11.33) and 4.46 (3.52-5.66) respectively], and was more or less constant thereafter [HR (95% CI) at 2, 5, 7 years = 2.01 (1.50-2.70), 2.19 (1.80-2.67) and 2.26 (1.70-2.99) respectively] (**Table 2**). Separate analyses for DVT and PE resulted in HRs similar to those for VTE.

Table 3 lists the HRs for VTE by patient, tumor and treatment characteristics. Older age at diagnosis, BMI $\geq$ 25 kg/m^2, pre-existing VTE, tumor size > 40 mm, progesterone receptor (PR) negative disease, > 4 affected lymph nodes and chemotherapy were all associated with an increase in VTE risk in multivariable analyses. Models with stepwise adjustment showed that the impact of patient, tumor and treatment characteristics was robust, except for comorbidities and breast-conserving surgery which showed no association with VTE after multivariable adjustment.

The proportional hazards assumption was not met for comorbid disease, PR status and chemotherapy **(Figure 2, Supplementary Table 3)**. While not reaching significance in terms of overall VTE risk, comorbid conditions were associated with late-onset events occurring 5 years after diagnosis. Similarly, PR-negative tumors showed a stronger association with late-onset VTE. Chemotherapy, on the other hand, was only associated with events occurring within the first year of diagnosis.

No major difference in risk was observed between chemotherapy alone and combined chemo- and endocrine therapy. VTE risks were also similar when comparing tamoxifen versus aromatase inhibitors (AIs) alone, but AI use tended to show a stronger association with VTE when combined with chemotherapy (**Supplementary Table 4**).

Sensitivity analyses using a more refined definition generated somewhat lower VTE rates, but HRs consistent with those observed in the main analysis **(Supplementary Table 5)**. The long-term VTE

risk remained present when censoring person-time at disease recurrence and new breast cancer diagnoses: i.e. the risk associated with the primary tumor was only slightly attenuated 7 years after diagnosis with a HR of 1.76 **(Supplementary Table 6)**. Relative risks of VTE were also similar in analyses excluding patients with a VTE history **(Supplementary Table 7)**, as were associations with individual patient, tumor and treatment characteristics **(Supplementary Table 8)**.

Discussion

In this population-based study, we demonstrate that breast cancer patients are at highest VTE risk within the first year of diagnosis, but remain at 2-fold increased risk for many years after. Older age at diagnosis, being overweight, VTE history, comorbid conditions, a larger tumor size, PR-negative disease, lymph node involvement, and receipt of chemo- and endocrine therapy were all independent predictors of VTE in breast cancer patients. The impact of most predictors was constant over time except for chemotherapy, comorbid disease and PR status, which showed differential associations with early and late-onset events.

Consistent with previous reports [3, 4, 9], the incidence of VTE was highest in the first 6 to 12 months after diagnosis. The observed absolute risks are also similar to recent estimates reported by Walker et al.[10] incorporating in- and outpatient diagnoses. Long-term risk data, however, are scarce, although a Danish study [4] previously indicated a potential sustained increase in risk with HRs being significant beyond 2 years of diagnosis. Our study is the first to confirm the long-term risk of VTE in breast cancer patients, with relative risks remaining 2-fold increased for at least 7 years. Importantly, we could address the impact of the primary tumor, as recurrent disease and treatment can result in inflated long-term risk estimates.

The strong impact of chemotherapy on VTE risk is consistent with previous reports showing an excess risk in chemotherapy-treated patients, independent of cancer site and stage [4, 9, 26, 27]. Several mechanisms have been proposed for the high thrombogenic potential of chemotherapy, including damage to endothelial cell walls, decreased fibrinolytic activity of the blood and use of venous catheters for chemotherapy administration [28, 29]. In line with RCT data [12, 30] and observational data by Walker et al. [10], the effect of chemotherapy was limited to the period of active treatment. A higher VTE incidence was also found with endocrine therapy. Trials comparing tamoxifen versus AIs have reported higher VTE rates with tamoxifen use [13]. In this observational study, no difference by type of

endocrine treatment was found; although there was some tendency of a higher VTE risk with AI use in chemotherapy-treated patients. This could be the consequence of a higher baseline risk in postmenopausal AI users [10] and/or preferential prescriptions of AIs to patients for whom tamoxifen is contraindicated because of a personal or family history of thrombosis, or other VTE risk factors [31]. We also note the particular high risk of VTE in AI users who received chemotherapy, although the underlying mechanism is unclear and requires further investigation.

Markers of tumor aggressiveness have previously been linked to VTE risk [3, 10], but little is known about the independent contribution of tumor-specific factors after accounting for treatment effects. We found a positive association with tumor size and PR negative disease in multivariable analyses. Since both factors are established markers of disease recurrence [16, 17], these data agree with a close interplay between tumor progression and prothrombotic processes [18, 19]. The lack of association with ER status can be explained by the adverse effect of endocrine therapy, which might have offset a protective effect of ER-positive disease. Interestingly, the impact of PR-negative tumors was stronger for late-onset VTE. Although the nature of this temporal association remains to be determined, PR absence has been associated with resistance to endocrine therapy [32]. In addition, ER-positive/PR-negative tumors are characterized by more aggressive features and worse outcomes compared to ER-positive/PR-positive tumors [33]. Previous studies have also reported increased VTE rates with lymph node involvement [3, 10], but the predictive value of this tumor characteristic has been questioned due to lack of adjustment for chemotherapy [34]. Despite the slight attenuation in multivariable analyses, extensive nodal involvement remained an independent predictor of VTE in our study.

We further observed independent associations with older age and increasing BMI, which have been reported previously [3, 4, 10]. Comorbid disease also predicted VTE risk, but only 5 years after diagnosis. Since short-term VTE risk is dominated by breast cancer treatment, this could have masked an independent effect of comorbid disease early after disease onset. The lack of a gradual increase in VTE risk with increasing comorbidity burden suggests that specific conditions are likely to have a

stronger influence than an aggregated score, which could be evaluated further in future larger scale studies.

Thromboprophyaxis leads to a reduction in VTE incidence in cancer patients [35, 36], but is not recommended on a routine basis in breast cancer patients due to the low baseline risk and side effect associated with thromboprophyaxis, namely bleeding [37]. Selected high-risk patients, however, could potentially benefit from prophylactic or early detection measures. Several risk prediction models have been developed for identifying high-risk patients, of which the Khorana model is the most established [38]. Although this model includes cancer site, it does not account for cancer-specific risk factors. Since VTE risk profiles differ by cancer site [10, 39], cancer specific models are needed in order to optimize risk assessment. The clinical predictors identified by our study may thus facilitate future risk stratification in the breast cancer setting. Further studies, however, are needed to assess the added value of other laboratory parameters, such as leukocytosis and thrombocytosis, on top of the risk predictors identified here.

The present study is characterized by a large population-based design and linkage to register-based data which minimizes information bias. Other strengths are the detailed information on patient, tumor and treatment characteristics and use of FPM for capturing time-dependent effects. We also acknowledge several limitations. Although the Patient Register has high validity for cardiovascular diagnoses including VTE, misclassification may have occurred. In agreement with previous reports [40, 41], ~89% of all cases were confirmed using prescription and death records. Sensitivity analyses showed no evidence of differential misclassification, despite the somewhat lower absolute rates. Second, outpatient diagnoses are only registered from 2001 onward. For this reason, some patients treated as disease-free may have had a VTE history at diagnosis. Risk estimates were, however, not materially different after excluding patients with pre-existing VTE. Third, BMI was the only variable assessed after diagnosis. We cannot rule out post-diagnostic changes in BMI, but class effects are considered unlikely. The observed association with overweight is also consistent with previous data [10].

Finally, it should be noted that cancer patients are subject to increased medical surveillance, resulting in inflated HRs close to diagnosis. This bias is unlikely to extend beyond 1 year of follow-up, and cannot explain the long-term risk pattern observed.

In conclusion, our study confirms the long-term VTE risk in breast cancer patients, and identifies a comprehensive set of clinical risk predictors, which may facilitate future risk stratification and prevention efforts. Our findings also provide novel insights into the time-dependent etiology of VTE in breast cancer patients, underscoring the importance of early and late-onset differentiation in VTE risk prediction.

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Figure legends

Figure 1. Cumulative incidence of VTE in breast cancer patients as compared to age-matched reference individuals from the general population.

Abbreviations: CI = confidence interval; HR = hazard ratio. Cumulative incidence estimates as obtained with Kaplan-Meier survival analysis with time since index date as underlying time scale.

Figure 2. Time-dependent effects of comorbidity, PR-negative disease and chemotherapy on VTE risk in breast cancer patients.

Abbreviations: CI = confidence interval; HR = hazard ratio. Time-dependent hazard ratios as estimated with flexible parametric survival models with time since diagnosis as underlying time scale: A = comorbid conditions (REF = no comorbid disease); B = Progesterone receptor (PR) status (REF = PR-positive tumors); C = chemotherapy (REF = no chemotherapy). All hazard ratios are multivariable adjusted.

Table 1. Characteristics of the study population.

Characteristics	**Breast cancer cohort (N = 8338) ***	**Matched population cohort (N = 39013)**
Age at diagnosis (years)		
Mean (SD)	57.1 (10.3)	57.3 (10.2)
Min-Max	25-75	25-75
Years of follow-up, median (IQR)	7.2 (4.3) / 5.3 (4.1)	5.9 (4.0)
No. of events:		
VTE	426 / 364	555
Pulmonary embolism	179 / 141	227
Deep vein thrombosis	262 / 235	358
Age at VTE diagnosis (years), mean (SD)	62.9 (10.4) / 62.0 (10.1)	65.3 (9.2)

Abbreviations: CI = confidence interval; ICD = international classification of diseases; SD = standard deviation; IQR = interquartile range; VTE = venous thromboembolism * For the Stockholm-Gotland breast cancer cohort, descriptive statistics of incident VTE are given for the entire follow-up in case only analysis (until 31 December 2012), and the end of follow-up in matched cohort analysis (until 31 December 2010) Descriptive statistics of incident VTE in the age-matched population cohort are given until 31 December 2010 (matched cohort analysis).

Table 2. Relative risk of venous thromboembolism in breast cancer patients compared to age-matched reference individuals from the general population, overall and at specific time points after the index date.

		HR (95% CI)						
		Overall	**At 6 months**	**At 1 year**	**At 2 years**	**At 5 years**	**At 7 years**	**At 9 years**
	N total/VTE *							
Matched population cohort	39013/555	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8338/364	3.28 (2.87-3.74)	8.62 (6.56-11.33)	4.46 (3.52-5.66)	2.01 (1.50-2.70)	2.19 (1.80-2.67)	2.26 (1.70-2.99)	2.19 (1.55-3.09)
	N total/DVT *							
Matched population cohort	39013/358	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8338/235	3.25 (2.75-3.83)	9.81 (6.70-13.81)	3.68 (2.64-5.13)	1.69 (1.17-2.43)	2.07 (1.58-2.71)	2.24 (1.54-3.25)	2.22 (1.42-3.47)
	N total/PE *							
Matched population cohort	39013/227	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8338/141	3.09 (2.50-3.81)	7.21 (4.62-11.26)	4.68 (3.26-6.71)	2.55 (1.67-3.87)	2.25 (1.70-2.99)	2.23 (1.48-3.37)	2.12 (1.25-3.61)

Abbreviations: HR = hazard ratio; CI = confidence interval; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism. Hazard ratios as estimated using flexible parametric survival models. Follow-up started from the breast cancer diagnosis and corresponding index date in the age-matched reference individuals and follow-up was complete until December 2010. * No. of incident VTE events is lower than in the Stockholm-Gotland breast cancer cohort with extended follow-up until December 2012.

Table 3. Association of patient, tumor and treatment characteristics with risk of venous thromboembolism risk in breast cancer patients.

		HR (95% CI)		
	N total/VTE	**Model 1**	**Model 2**	**Model 3**
Patient characteristics				
Age at diagnosis (years)				
< 50	1857/66	REF (1.00)	REF (1.00)	REF (1.00)
50-59	2639/119	1.21 (0.90-1.64)	1.24 (0.91-1.67)	1.35 (0.99-1.83)
60-69	2875/174	1.73 (1.30-2.30)	1.70 (1.28-2.26)	1.98 (1.47-2.66)
> 69	967/67	2.11 (1.50-2.97)	1.79 (1.27-2.54)	2.17 (1.51-3.14)
BMI (kg/m^2)				
<25	2546/94	REF (1.00)	REF (1.00)	REF (1.00)
25-30	1557/79	1.38 (1.02-1.86)	1.38 (1.02-1.86)	1.37 (1.01-1.85)
> 30	584/37	1.71 (1.17-2.50)	1.64 (1.11-2.40)	1.60 (1.09-2.35)
Pre-existing VTE				
No	8189/382	REF (1.00)	REF (1.00)	REF (1.00)
Yes	149/44	11.06 (8.08-15.14)	10.69 (7.80-14.66)	11.56 (8.39-15.92)
Comorbidities *				
None	7385/360	REF (1.00)	REF (1.00)	REF (1.00)
1	514/38	1.42 (1.02-2.00)	1.27 (0.90-1.77)	1.28 (0.91-1.80)
≥ 2	439/28	1.30 (0.88-1.92)	1.14 (0.77-1.69)	1.16 (0.78-1.73)
Tumor characteristics				
Tumor size (mm)				
≤ 10	2086/93	REF (1.00)	REF (1.00)	REF (1.00)
11-20	3555/174	1.14 (0.88-1.46)	1.14 (0.88-1.49)	1.08 (0.83-1.41)
21-40	1924/106	1.37 (1.04-1.81)	1.20 (0.88-1.63)	1.13 (0.83-1.55)
>40	514/43	2.22 (1.55-3.20)	1.71 (1.15-2.53)	1.55 (1.02-2.35)
Tumor grade (Elston)				
Low	963/38	REF (1.00)	REF (1.00)	REF (1.00)
Moderate	2557/119	1.19 (0.83-1.71)	1.03 (0.71-1.49)	0.95 (0.65-1.38)
High	1539/73	1.35 (0.91-2.00)	1.01 (0.66-1.54)	0.85 (0.56-1.31)
Estrogen receptor status				
Positive	6353/313	REF (1.00)	REF (1.00)	REF (1.00)
Negative	1376/76	1.22 (0.95-1.57)	0.96 (0.71-1.31)	1.06 (0.66-1.70)
Progesterone receptor status *				
Positive	5176/236	REF (1.00)	REF (1.00)	REF (1.00)
Negative	2419/143	1.38 (1.12-1.70)	1.32 (1.03-1.70)	1.33 (1.03-1.71)
No. of affected lymph nodes				
0	5033/225	REF (1.00)	REF (1.00)	REF (1.00)
1-4	2241/113	1.21 (0.97-1.52)	1.16 (0.92-1.47)	0.99 (0.76-1.28)
> 4	714/67	2.53 (1.92-3.33)	2.18 (1.62-2.94)	1.73 (1.21-2.46)
Treatment characteristics				
Surgery				
Total mastectomy	3205/178	REF (1.00)	REF (1.00)	REF (1.00)
Breast-conserving	5014/242	0.81 (0.67-0.98)	0.79 (0.62-1.01)	1.08 (0.81-1.45)
Radiotherapy				
No	1882/89	REF (1.00)	REF (1.00)	REF (1.00)
Yes	6318/330	1.16 (0.92-1.46)	1.32 (0.99-1.76)	1.07 (0.79-1.47)
Chemo/endocrine therapy *				
None	355/11	REF (1.00)	REF (1.00)	REF (1.00)
Endocrine only	4475/208	1.60 (0.87-2.94)	1.59 (0.87-2.92)	1.86 (0.94-3.72)
Chemo only	1119/66	2.77 (1.45-5.26)	2.58 (1.35-4.93)	2.42 (1.24-4.73)
Chemo plus endocrine	2230/131	2.67 (1.43-4.97)	2.45 (1.31-4.58)	2.74 (1.33-5.63)

Abbreviations: BMI = body mass index, CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism. Hazard ratios as estimated from Cox proportional hazard models with time since diagnosis as underlying time scale. Model 1: adjusted for age at diagnosis; Model 2: grouped models including respectively all patient, tumor and treatment characteristics with additional adjustment for age at diagnosis; Model 3: multivariable adjusted models including all variables listed in the table. * Variables not meeting the proportional hazards assumption.