When are breast cancer patients at highest risk of venous thromboembolism: A cohort study using English healthcare data

Short title: VTE in breast cancer

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Key Points

1. Breast cancer patients have a risk of VTE equivalent to 6% a year whilst undergoing chemotherapy and in the month following treatment.

2. Tamoxifen is associated with a risk of VTE equivalent to 2% a year, which is 4-times higher than the risk before commencing therapy.

Abstract

Breast cancer patients are at increased risk of VTE, particularly in the peri-diagnosis period. However, no previous epidemiological studies have investigated the relative impact of breast cancer treatments in a time-dependent manner. We aimed to determine the impact of breast cancer stage, biology and treatment on the absolute and relative risks of VTE, using several recently linked data sources from England. Our cohort comprised 13,202 breast cancer patients from the Clinical Practice Research Datalink (linked to Hospital Episode Statistics and Cancer Registry data), diagnosed between 1997 and 2006 with follow-up continuing to the end of 2010. Cox regression analysis was performed to determine which demographic, treatment-related and biological factors independently affected VTE risk. Women had an annual VTE incidence of 6% whilst receiving chemotherapy which was 10.8-fold higher (95% CI, 8.2 to 14.4; absolute risk (AR) =59.6 per 1000 person-years) than women who did not receive chemotherapy. Following surgery the risk was significantly raised in the first month (HR=2.2; 95% CI 1.4 to 3.4; AR=23.5; reference group, no surgery), but it was not raised subsequent to this. Risk of VTE was noticeably higher in the 3-months following initiation of Tamoxifen compared with the risk before therapy (HR=5.5; 95% CI 2.3 to 12.7; AR=24.1), however commencement of aromatase inhibitors was not associated with VTE (HR=0.8; 95% CI 0.5 to 1.4; AR=28.3). In conclusion, women receiving chemotherapy for breast cancer have a clinically important risk of VTE, whilst an increased risk of VTE immediately following endocrine therapy is restricted to Tamoxifen.

Introduction

Women with breast cancer have a 3-4 fold increased risk of VTE compared to women of an equivalent age without cancer.[1,2] As breast cancer is the most common cancer worldwide,[3] this equates to a substantial impact of breast cancer-related VTE for patients and medical resources. Breast cancer associated VTE accounts for approximately 17% of cancer-related VTEs presenting to anticoagulation clinics.[4] It is also associated with increased disease recurrence,[5] but more importantly reduced survival,[5,6] among a patient group for whom prognosis is otherwise comparatively good.

Previous cohort studies have identified several risk factors for VTE in breast cancer patients including metastatic disease,[2,7,8] chemotherapy[2,8,9] and Tamoxifen treatment.[10] A recent systematic review demonstrated that on average, breast cancer patients selected because they had either metastatic disease or were undergoing surgery or chemotherapy had a 10-fold increase in VTE risk compared to the breast cancer population as a whole.[11] While these studies go some way to highlighting which groups are at highest risk of VTE, none have comprehensively assessed the relative importance of cancer treatments and biology in influencing VTE risk using prospectively gathered data.

Identifying combinations of between and within patient factors would allow us to develop algorithms to guide thromboprophylaxis in the setting of breast cancer. Guidelines issued by the National Comprehensive Cancer Network (NCCN) emphasise that general use of thromboprophylaxis in patients receiving chemotherapy remains controversial and that more data are needed before risk-adjusted thromboprophylaxis can be routinely introduced in clinical practice.[12] Guidelines from the American College of Chest Physicians (ACCP) also advise against routine prophylaxis for cancer outpatients unless they have additional risk factors including previous thrombosis, immobilisation, hormonal therapy and angiogenesis inhibitors, a recommendation based on low grade evidence.[13] In both instances, there is limited guidance for specific cancer types (including breast) between which the influence of other risk factors could vary substantially. Identifying these patients most at risk is problematic owing in part to the absence of

precise and accurate data on absolute risks of VTE during specific times of their disease course. We have addressed this by ascertaining the incidence rate of VTE in relation to tumour biology (cancer grade and stage), intrinsic patient factors (age, body mass index (BMI) and comorbidity) and cancer treatments (surgery, chemotherapy and endocrine therapy) using four recently linked healthcare databases from the UK.

Methods

Patients and data sources

We utilised data from four linked healthcare sources. The Clinical Practice Research Datalink (CPRD) is a prospectively gathered, anonymised primary care database using data from more than 600 GP practices in the UK from 1987 onwards. It provides all recorded primary care data on patients including clinical diagnoses and prescriptions and is known to be broadly representative of the UK population in terms of age, sex, socioeconomic and geographic distribution.[14] Hospital Episodes statistics (HES) is a secondary care database containing data for all hospitalisations in England, including primary and secondary discharge diagnoses and inpatient procedures. Information on cancer diagnoses was obtained from the National Cancer Intelligence Network (NCIN) which processes data supplied by all regional cancer registries in the UK. [15] Two related but separate databases make up the cancer registry data; the Merged Cancer Registry data (from English registries only) and the Office of National Statistics (ONS) minimum cancer dataset. Detailed information on specific data items collected by cancer registries in England for breast cancer patients over the period of this study (1997 to 2006), along with the completeness of recording for each of the TNM components we used to define cancer stage can be found elsewhere.[16] Finally, we used death certificate data from the ONS which provides information on dates and underlying causes of death. The present analysis is based on patients from approximately 50% of CPRD practices in England for whom data linked to the HES, NCIN and ONS data sources are available from April 1997 onwards. The study received approval from the CPRD Independent Scientific Advisory Committee (protocol no. 10_091).

We selected all patients who had a first breast cancer diagnosis (ICD-10 code C50) between 1st April 1997 and 31st December 2006. Patients were followed up until they developed a VTE event, died, left a participating GP practice or 31st December 2010, whichever was earliest. The earliest recorded date in the cancer registry data was used to determine date of cancer diagnosis. Patients were excluded if they were:

- Male
- Under 18 years of age

- Not in a linked general practice.
- Diagnosed with breast cancer outside of the CPRD and HES registration periods
- Diagnosed in the first year of registration at a participating practice.
- Had a VTE prior to first cancer diagnosis

Risk Factors

Cancer stage and grade at diagnosis were obtained from the cancer registry database. Where known, we classified stage as either "local disease" (confined to the breast), "regional disease" (axillary lymph node involvement), or "distant metastases" (any evidence of distant metastases). Conversion from TNM staging into these summary stages was carried out according to the algorithm designed by Ording et al.[17] Cancer treatments were defined on the basis of an associated OPCS-4 code for chemotherapy and surgery using the hospital admissions data. Surgery codes were specific to procedures used in the treatment of breast cancer. For chemotherapy, events were frequently recorded as a series of day case or outpatient procedures and were considered as part of the same course of treatment when occurring within 28 days of each other. Broad OPCS-4 codes for chemotherapy were used, limiting our potential to study specific chemotherapy regimens. We distinguished endocrine treatment with Tamoxifen from the newer aromatase inhibitors (AI), both of which were obtained from the GP prescription record. We assumed that women without endocrine prescriptions had oestrogen receptor negative breast cancer. BMI was determined from GP records based on the most recent recording prior to cancer diagnosis, whilst GP records were also used to calculate an individual comorbidity score (Charlson index but ignoring the breast cancer diagnosis which was universal in our cohort) for each patient (coded as 0,1-3,≥4).[18]

Outcome

Primary care (CPRD) medical diagnoses were recorded using Read codes and secondary care (HES) diagnoses using ICD-10 codes. A VTE event was confirmed when a medical code for venous thromboembolism (ICD 10; I26, I80-I82) in either or both the CPRD and HES was supported by either an anticoagulant prescription or medical code providing evidence of anticoagulation if either were recorded between 15 days before and 90 days after the VTE event date, or if death occurred

within 30 days of the event. Additionally, an underlying cause of death of VTE was included as evidence of a valid VTE event. Only the first VTE event following the cancer diagnosis was considered as follow-up would cease at this time, therefore all subsequent VTE events were ignored. This algorithm for defining VTE has been previously validated using primary care data alone, although this validation was carried out in women who developed VTE following oral contraceptive use rather than in women with breast cancer.[19]

Statistical methods

Absolute risks of VTE (per 1000 person years) were calculated on the basis of all risk factors listed above by dividing the number of people with VTE by the person-time at risk. To establish the independent effects of these risk factors, Cox regression was used to obtain adjusted hazard ratios. BMI, comorbidity, cancer stage and cancer grade were all treated as time-independent covariates whilst the effects of cancer treatments were allowed to vary by time. Each variable was examined on its own within the breast cancer cohort, and then adjusted for all other variables in the model regardless of their own significance. Adjusted hazard ratios were presented in the results text.

For surgery and chemotherapy, we then assessed the absolute VTE risk i) before treatment, ii) during treatment, and iii) in monthly periods post treatment. For endocrine treatment, we assessed the risk i) before therapy, ii) in the three month interval following the initial prescription and iii) subsequent follow-up time, periods selected to account for the fact that endocrine therapy is usually administered continuously for a minimum of 5 years. For all treatment variables patients who did not undergo the treatment comprised the reference category. Whilst date of cancer diagnosis was always used to denote study entry, calendar time was used as the timescale for our analysis so that both the unadjusted and adjusted hazard ratios would account for any temporal confounding.

In subsequent analyses we looked at the joint relationship between surgery and chemotherapy, to account for the fact that chemotherapy often takes place during the time in which women are recovering from surgery. By assuming a long period of excess VTE risk following surgery or chemotherapy completion (3 months), this allowed us to explore absolute risks in the absence of potential carry-over effects from the other treatment. We also looked at the interaction between

cancer stage and the effects of surgery and chemotherapy. There were missing data in our cohort for cancer stage, grade and body mass index. We accounted for these missing data by creating a category comprising women with missing data. When analyses were repeated using multiple imputation by chained equations to impute missing values, results were very similar. All analyses used Stata version 13 (Statacorp, College Station, Texas).

Results

Patient characteristics

A total of 13,202 women were diagnosed with breast cancer between 1997 and 2006 (Table 1). Women were a median age of 62 years at cancer diagnosis (IQR, 52 to 74 years). A total of 4% had metastatic disease at diagnosis and 38% had local disease (with stage unknown for 36% of women). 77% of the sample underwent surgery at some point following cancer diagnosis, 21% underwent chemotherapy and 82% were prescribed endocrine therapy. First surgery occurred on average 17 days (IQR, 0 to 31) after cancer diagnosis. Among women who had primary surgery for breast cancer, chemotherapy began an average of 52 days (IQR 33 to 105) after surgery. The median follow-up time from diagnosis was 5.3 years (IQR 2.8, 8.0 years). VTE occurred in 611 cases among 72,596 person-years of follow-up corresponding to a rate of 8.4 per 1000 person years (95% confidence Interval, CI, 7.8-9.1). This rate was 3.5 times (95% CI, 3.2 to 3.9) higher than in age matched controls as shown in our previous paper from this cohort.[1] The rate of VTE in breast cancer patients increased over the time period of the study from 5.4 per 1,000 person-years (3.6 to 8.2) for women with breast cancer diagnosed in 1997 to 10.5 per 1,000 person-years (8.5 to 13.2) for 2005. Of the VTE events, there were 273 women who developed PE either with or without DVT, 314 who developed DVT alone and 24 other thrombosis events. In most instances, the type of DVT was not specified (n=175), where this was specified 13 out of 139 events were upper extremity events.

Demographic and tumour related factors and risk of VTE

Increased age and BMI were significant predictors of VTE (Table 2). VTE risk increased with age, with women aged 80 years or over at diagnosis having five times the risk compared with younger women (adjusted HR=5.0; 95% CI, 3.0-8.2; absolute rate (AR), 14.9 per 1,000 person-years). BMI had a similarly large influence on VTE risk, with the highest rate in women who were morbidly obese (BMI≥40kg/m^2) (HR=3.0; 95% CI, 2.1-4.4; AR, 16.5; reference group, BMI 18.5-25.0 kg/m^2). Whilst the rate of VTE was higher in women with metastatic cancer (18.2 per 1,000 person-years) compared to those with local disease (6.8 per 1,000 person-years), this was in part due to the higher mean age among women with metastatic disease (66.3 years, SD 15.1) compared with local disease

(61.3 years, SD 12.8) and that more women with metastatic disease underwent chemotherapy (27.0%) than with local disease (15.2%). When these two variables alone were adjusted for the hazard ratio for metastatic disease decreased from 2.5 (95% CI, 1.6-4.0) in the univariable model to 1.5 (95% CI, 1.0-2.5). Similarly, a higher absolute rate of VTE among women with a high Charlson score (≥4), could be largely accounted for by the higher mean age among women with a Charlson score ≥4 (72.0 years, SD 13.0) than those with a Charlson score of 0 (60.6 years, SD 14.5).

Surgery and risk of VTE

Surgery in this cohort took the form of either mastectomy (with 9.1% having immediate reconstruction) or a breast-conserving procedure. When other factors were accounted for a significantly increased risk compared with those not undergoing surgery only existed in the first month following discharge from the surgical admission (HR=2.2; 95% CI, 1.4 to 3.4; absolute rate =23.5 per 1,000 person-years) (Table 2). Rates of VTE following surgery did not vary by stage (monthly rates ranging from 17 to 28 per 1,000 person-years; Table 3; Test for interaction between surgery and stage, P=0.15).

Chemotherapy and risk of VTE

Women who underwent chemotherapy had very high absolute risks of VTE both during chemotherapy and in the month following cessation of therapy (both >50 per 1,000 person-years)(Table 2). The adjusted hazard ratios compared to no chemotherapy were 10.8 (8.2 to 14.4) during chemotherapy and 8.4 (4.9-14.2) in the month afterwards. The risk of VTE remained high in the second month following completion of therapy, but by 3 months the risk had reverted to that before treatment (Figure 1). The adjusted hazard ratio during chemotherapy compared to time before chemotherapy in the same patients was 6.6 (95% CI, 4.3 to 10.1). The effect of stage on risk of VTE was more pronounced during follow-up time outside of chemotherapy (HR=2.5 for metastatic disease; 1.6 to 4.2), with a significant interaction between stage and chemotherapy treatment (P=0.004)(Table 3).

Independent effects of stage, surgery and chemotherapy

When looking at chemotherapy and surgery jointly, the absolute risk of VTE was particularly high when surgery took place in the 2 month chemotherapy recovery period, however, this was based on a small number of events and as such the confidence interval was wide (AR=92.1; 38.3 to 221.2)(Table 4).

Endocrine therapy and risk of VTE

In the three months following commencement of endocrine therapy, the risk of VTE was more than double the risk in those who did not receive endocrine therapy (HR=2.4; 95% CI 1.7 to 3.4; AR=27.7)(Table 2). No increased risk was observed beyond three months of therapy (HR=0.9; 95% CI 0.7 to 1.1; AR=7.0).

When absolute risks were explored on the basis of type of endocrine therapy there were important differences between Tamoxifen and AIs (Table 5). VTE risk increased more than 5-fold in the 3 months following commencement of therapy among women who received Tamoxifen only (HR=5.5; 95% CI 2.3 to 12.7; AR=24.1; reference category – risk before commencing Tamoxifen). After 3 months a non-significant 2-fold increase in risk remained (HR=1.9; 95% CI 0.9 to 4.3; AR=5.2). Specific adjustment for chemotherapy (which occurred frequently in the cohort time prior to Tamoxifen) accounted for most of the difference between the univariable and multivariable results (HR=1.1 vs. HR=1.9). In contrast to Tamoxifen, among those receiving an AI only, there was no increase in risk in the three months after starting therapy (AR=0.8; 95% CI 0.5 to 1.4; AR=28.3; reference category – risk before commencing AIs). Furthermore, we found that among women who switched to an AI after initially taking Tamoxifen, the absolute risk following commencement of the AI was similar to that in the period before commencement of the AI (subsequent time for Tamoxifen, Table 5).

Discussion

It is known that women with breast cancer have a 3.5 fold increased risk of VTE compared to women of a similar age without cancer.[1,2] A risk of this magnitude would not justify continuous VTE prophylaxis and thus it becomes important to identify subgroups of patients and time where the risk is highest. Using routinely available data from primary care, secondary care and UK cancer registries we report high risks of VTE among women undergoing chemotherapy and in the first three months of treatment with Tamoxifen. During chemotherapy the risk of VTE was raised more than 10-fold and this risk remained high in the 2-months following completion of treatment. Among women who commenced Tamoxifen, the risk of VTE was 5-times higher than it was in the period before commencing therapy. We also observed a doubling of rates of VTE in women with breast cancer over the 10-year period of the study. This is consistent with reports of an increase in risk of cancer-associated VTE over time in both this and other populations, a trend which may be due to either more aggressive cancer treatments or ascertainment resulting from greater knowledge of the link between cancer and thrombosis. [1,20–22]

This report contained both absolute risks (unadjusted) and adjusted hazard ratios. Interpretation of absolute risks and associated unadjusted hazard ratios may be more useful in terms of clinical decision making if made on the basis of a single factor. However, we observed that unadjusted and adjusted hazard ratios were always similar except in two specific instances where highlighted (chemotherapy and stage; age and comorbidity). In a stratified analysis involving stage and chemotherapy, we reported a much higher risk of VTE with metastatic disease compared with local disease within time periods not influenced by chemotherapy (unadjusted HR of 3.2 and adjusted HR of 2.5). However, during chemotherapy and immediately afterwards, rates of VTE were high regardless of stage although these estimates were based on small event numbers.

Our observed rate of 8.4 per 1000 person years was similar to that reported by Chew et al. in the largest study carried out to date on VTE risk in breast cancer.[7] In our study, we were also able to look at several risk factors absent from the Californian study including detailed and accurate recording of chemotherapy treatment and use of endocrine therapy, as well as BMI. Furthermore,

our study contained a longer average follow-up duration (5.5 years) than both the Californian and other comparable studies[2,8,9] and we were able to assess the effects of surgery and chemotherapy in a time dependent manner in a way which has evaded previous research.

Chemotherapy is known to be an important risk factor for VTE in cancer patients. Previously in relatively small cohorts of women receiving chemotherapy for breast cancer, risks of VTE have ranged from 5.5 to 8.0% among women with loco-regional disease[5,23,24] and from 4.4 to 17.7% in women with metastatic disease.[23,25,26] Using data on 2,773 women undergoing chemotherapy for breast cancer, we reported a risk of VTE which was the equivalent of 5-6 percent a year both during chemotherapy and in the month after therapy (with 3.7% of women undergoing chemotherapy developing a VTE either during treatment or the 3 months following completion). The risk during therapy was 6.6-times higher than in the same women before therapy when adjusted for other treatment factors. A validated risk prediction tool has been developed to determine which patients undergoing chemotherapy are at highest risk and could therefore benefit from prophylaxis.[27] However, neither that study nor a more recent extension[28] of the score was able to demonstrate the periods of highest risk for patients, and since both required informed consent they were likely to exclude those with the poorest performance status.

We found that the risk of VTE was around 2-fold higher following discharge after surgery; however the risk was only increased for the month following surgery once other factors were accounted for and the magnitude of the increase was much less than following chemotherapy. This smaller effect may in part reflect the minimal-invasiveness of breast cancer surgery which does not penetrate body cavities, particularly in an era when breast reconstruction was less frequently performed. Whilst 70-80% of UK breast surgeons in this era prescribed anticoagulant thromboprophylaxis to breast cancer patients undergoing surgery, our increased risk was observed in the time following discharge in which thromboprophylaxis is not usually administered.[29] Despite limited numbers, we demonstrate a particularly increased risk of VTE associated with surgery following chemotherapy. As neoadjuvant chemotherapy is increasingly being used, that has important implications for surgical thromboprophylaxis in the neoadjuvant setting.

Tamoxifen is a widely recognised risk factor for VTE. The magnitude of increase in risk of VTE we observed following commencement of Tamoxifen is comparable with studies comprising women with early stage breast cancer reported between 1989 and 1999, which report an excess risk of VTE events in women receiving Tamoxifen of between 1.5-fold and 7-fold.[30] Our results are also concordant with those from a large cohort of women with early stage breast cancer from Denmark where Tamoxifen treated women had a 3.5-fold higher risk of VTE than women receiving other treatments.[10] Previous research has found the influence of Tamoxifen on risk of VTE to attenuate 1-2 years after commencement of therapy,[10,31] possibly suggesting an adaptation of the haemostatic system to the procoagulant effects of Tamoxifen. This is the first study to demonstrate that the prothrombotic effects of Tamoxifen are noticeably reduced after only 3 months of treatment. More recently, AIs have become more commonly used however the impact of these on the risk of VTE is less clearly established.[32] In observational research such as this, a direct comparison of VTE risks between Tamoxifen and AIs is complicated by the fact that prescriptions for AIs were until quite recently limited to higher risk patients because of the high cost of on-patent drugs, as evidenced by the very high baseline rate of VTE among this group. In addition, patients receiving AIs are likely to be an older group, as AI use, unlike Tamoxifen, is limited to post-menopausal women.

A limitation of our study is that whilst we had a large sample size overall, looking at risks on the basis of more intricate combinations of risk factors was hampered by small numbers of events. For instance, whilst we found the risk of VTE was high in women undergoing surgery shortly after chemotherapy, only five VTE events occurred during this period and hence the confidence interval around the absolute risk was wide. Our results also need to be interpreted in light of the fact that data on cancer stage could not be determined for around one third of our sample. This reflects our reliance on routinely collected data where this level of recording is standard. However, among those who did have data on stage, five-year survival rates among women with localised (88%) and metastatic disease (27%) in our study were consistent with published data from the US population.[33] As we have previously acknowledged, our algorithm for defining VTE was not validated specifically in cancer patients and would not capture anticoagulant prescriptions emanating from secondary care.[1] However, the usual requirement is for cancer patients to receive continuous anticoagulant

therapy for a minimum of 3 months following the primary VTE and such prescriptions would be captured in primary care. Furthermore, previous studies using administrative data have relied solely on physician coding of VTE without requiring evidence of anticoagulation.[7,8,10,34] Previously, our algorithm was shown to have a positive predictive value of 84% when using VTE codes from primary care only.[19] Whilst this is higher than studies which have relied solely on administrative codes for defining VTE,[35–37] it could still indicate that some of our VTE cases are liable to be false positives, which if greater than the number of VTE cases not captured by our algorithm would result in a slight overestimation in absolute rates of VTE in each exposure category. A Further limitation of our work includes the lack of data on thromboprophylaxis occurring during inpatient episodes, whether this be for cancer treatments (e.g. surgery) or complications of the malignancy. However, thromboprophylaxis specifically for systemic cancer treatment was rare based on a questionnaire survey conducted during this study period.[38] In addition, ambulatory thromboprophylaxis with aspirin is likely to have been obtained predominantly over the counter for the current study cohort (who had a median age of 62 years) so this would also not be reliably captured via our primary care data. Finally, we relied on adjustment for Charlson index to account for any confounding due to underlying health status. Whilst one could argue that this would be less exhaustive than adjusting for specific health indices which influence VTE risk, we found that adjusting for Charlson score had very minimal impact on the effect sizes observed for other variables of interest. Consequently, we believe it is very unlikely that adjustment for additional health-related variables would explain much of the large increase in risk we observed following chemotherapy and Tamoxifen initiation unless the Charlson score was to be a particularly poor indicator of morbidity which has been proved not to be the case.[39]

Breast cancer is the most common cancer worldwide, with women in the UK specifically having a 1 in 8 lifetime risk of developing breast cancer.[40] The financial and human impact of breast cancer-related VTE therefore means that identifying women who are most at risk and would potentially benefit from prophylactic intervention is vital. Our data was able to address this by demonstrating that whilst chemotherapy is known to increase the risk of VTE in both breast and other cancers, this risk remained high for two months following completion of the final course of therapy, and that this

risk may be increased further where it is commenced soon after surgery. Such detail can complement the recent ACCP and NCCN guidelines recommending prophylaxis for higher-risk outpatient cancer patients.[12,13] Speculation as to the absolute VTE risk above which prophylaxis is advised needs to take into account the harms (in particular bleeding) as well as benefits of prolonged anticoagulation, which is beyond the scope of the present work. Further observational research on this topic would benefit from the inclusion of information on laboratory data (e.g. haemoglobin and platelet counts) as well as more novel biomarkers which are not universally available in studies using electronic data recorded for administrative purposes. An attractive feature of our study, however, is that risks are presented based on easily ascertainable yet time-dependent risk factors, which we believe could form the basis of selection of appropriate patients for future randomised trials. Future research should focus on the development of prognostic models to identify specific women with breast cancer for whom the benefits of prophylactic intervention would outweigh the harms.

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Authorship Contributions

JW, TRC and MJG were responsible for the conception and design of the study. AJW was primarily responsible for the data management with input from CJC. AJW carried out the data analysis under the supervision of MJG. CCK provided advice relating to clinical aspects during all stages of the project (especially when planning analyses and interpreting results). AJW and MJG wrote the first draft of the manuscript, with all authors contributing to subsequent versions of the manuscript. All authors have seen and approved the final version.

Disclosure of Conflicts of Interest

None of the authors have conflicts of interest to declare.

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Table 1: Characteristics of breast cancer patients

		Number of patients		Number with VTE	
		N	%	VTE	% with VTE
Total		13,202		611	
Cancer stage	Local disease	5,037	38.2	214	4.3
	Regional disease	2,961	22.4	161	5.4
	Distant metastases	470	3.6	21	4.5
	Unknown	4,734	35.9	215	4.5
Grade	Well differentiated	1,681	12.7	71	4.2
	Moderately differentiated	4,232	32.1	196	4.6
	Poorly differentiated	3,024	22.9	166	5.5
	Unknown	4,265	32.3	178	4.2
Age (years)	<40	715	5.4	21	2.9
	40-49	2,030	15.4	63	3.1
	50-59	3,262	24.7	108	3.3
	60-69	2,973	22.5	179	6.0
	70-79	2,407	18.2	158	6.6
	≥80	1,815	13.8	82	4.5
Comorbidity	0	6,987	52.9	295	4.2
	1 to 3	5,860	44.4	293	5.0
	≥4	355	2.7	23	6.5
Body mass Index (kg/m^2)	Underweight (<18.5)	192	1.5	4	2.1
	Ideal (18.5-24.9)	3,099	23.5	93	3.0
	Overweight (25.0-29.9)	2,520	19.1	148	5.9
	Obese (30.0-39.9)	1,119	8.5	73	6.5
	Morbidly obese (≥40.0)	440	3.3	38	8.6
	Missing	5,832	44.2	255	4.4
Surgery	No	3,093	23.4	104	3.4
	Yes	10,109	76.6	507	5.0
Chemotherapy	No	10,429	79.0	422	4.1
	Yes	2,773	21.0	189	6.8
Endocrine therapy	No	2,323	17.6	87	3.7
	Yes	10,879	82.4	524	4.8

Table 2: Rates of VTE in relation to potential risk factors

				Absolute rates			Univariable Cox model			Multivariable Cox model[a]		
		Events	Person-time[b]	Rate[c]	95%	CI	HR	95%	CI	HR	95%	CI
Stage	Local disease (n=5,037)	214	31.4	6.8	6.0	7.8	Reference			Reference		
	Regional disease (n=2,961)	161	16.3	9.9	8.5	11.6	1.4	1.2	1.8	1.2	0.9	1.4
	Distant Metastases (n=470)	21	1.2	18.2	11.9	28.0	2.5	1.6	4.0	1.5	1.0	2.4
	Unknown (n=4,734)	215	23.8	9.0	7.9	10.3	1.3	1.1	1.6	1.2	0.9	1.4
Grade	Well differentiated (n=1,681)	71	11.1	6.4	5.1	8.1	Reference			Reference		
	Moderately differentiated (n=4,232)	196	25.1	7.8	6.8	9.0	1.3	1.0	1.7	1.1	0.8	1.5
	Poorly differentiated (n=3,024)	166	16.1	10.3	8.9	12.0	1.2	0.9	1.6	1.1	0.8	1.4
	Unknown (n=4,265)	178	20.3	8.7	7.6	10.1	1.6	1.2	2.1	1.3	1.0	1.7
Surgery	No surgery (n=3,093)	104	11.5	9.0	7.4	10.9	Reference			Reference		
	Before surgery	13	1.5	8.7	5.1	15.0	0.9	0.5	1.6	0.7	0.4	1.2
	During surgery hospitalisation	3	0.2	17.9	5.8	55.5	1.7	0.6	5.5	1.5	0.5	4.9
	1st month following discharge	26	1.1	23.5	16.0	34.5	2.4	1.6	3.8	2.2	1.4	3.4
	2nd month following discharge	24	1.0	24.3	16.3	36.2	2.4	1.5	3.8	1.4	0.9	2.2
	3rd month following discharge	12	1.0	12.6	7.2	22.2	1.2	0.7	2.2	0.6	0.3	1.1
	Subsequent time	429	56.3	7.6	6.9	8.4	0.9	0.7	1.1	1.0	0.8	1.3
Chemotherapy	No chemotherapy (n=10,429)	422	57.1	7.4	6.7	8.1	Reference			Reference		
	Before chemotherapy	31	2.7	11.7	8.2	16.6	1.5	1.0	2.1	1.6	1.1	2.4
	During chemotherapy	77	1.3	59.6	47.7	74.5	7.7	6.0	9.8	10.8	8.2	14.4
	1st month following completion	15	0.3	51.6	31.1	85.5	6.5	3.9	10.9	8.4	4.9	14.2
	2nd month following completion	8	0.2	33.1	16.6	66.3	4.0	2.0	8.1	4.5	2.2	9.3
	3rd month following completion	3	0.2	13.5	4.4	41.9	1.8	0.6	5.5	2.0	0.6	6.3
	Subsequent time	55	10.8	5.1	3.9	6.7	0.7	0.5	0.9	1.1	0.8	1.5
Endocrine therapy	No endocrine therapy (n=2,323)	87	9.8	8.9	7.2	11.0	Reference			Reference		
	Before endocrine therapy	54	3.0	17.8	13.7	23.3	1.9	1.3	2.6	1.2	0.8	1.7
	First 3 months of endocrine therapy	69	2.5	27.7	21.9	35.0	2.9	2.1	4.0	2.4	1.7	3.4
	Subsequent time	401	57.3	7.0	6.3	7.7	0.8	0.6	1.0	0.9	0.7	1.1
Body mass Index (kg/m^2)	Underweight (<18.5)(n=192)	4	1.1	3.8	1.4	10.1	0.7	0.3	2.0	0.7	0.3	1.9
	Ideal (18.5-24.9)(n=3,099)	93	18.3	5.1	4.2	6.2	Reference			Reference		
	Overweight (25.0-29.9)(n=2,520)	148	14.7	10.1	8.6	11.8	2.0	1.5	2.6	1.8	1.4	2.4
	Obese (30.0-39.9)(n=1,119)	73	6.4	11.4	9.1	14.3	2.2	1.6	3.0	2.1	1.6	2.9

	Morbidly obese (≥40.0)(n=440)	38	2.3	16.5	12.0	22.7	3.2	2.2	4.7	3.0	2.1	4.4
	Missing (n=5,832)	255	29.9	8.5	7.6	9.7	1.6	1.3	2.0	1.5	1.2	1.9
Age (years)	<40 (n=715)	21	4.1	5.1	3.4	7.9	Reference			Reference		
	40-49 (n=2,030)	63	12.7	5.0	3.9	6.3	1.0	0.6	1.7	1.1	0.7	1.8
	50-59 (n=3,262)	108	20.7	5.2	4.3	6.3	1.1	0.7	1.7	1.3	0.8	2.1
	60-69 (n=2,973)	179	17.7	10.1	8.7	11.7	2.1	1.3	3.3	2.9	1.8	4.6
	70-79 (n=2,407)	158	11.9	13.3	11.4	15.5	2.7	1.7	4.2	4.2	2.6	6.7
	≥80 (n=1815)	82	5.5	14.9	12.0	18.4	2.9	1.8	4.7	5.0	3.0	8.2
Charlson index	0 (n=6,987)	295	37.5	7.8	7.1	8.8	Reference			Reference		
	1 to 3 (n=5,860)	293	33.6	8.7	7.8	9.8	1.1	1.0	1.4	1.0	0.8	1.1
	≥4 (n=355)	23	1.5	15.4	10.2	23.1	2.1	1.4	3.3	1.3	0.9	2.1

a Hazard ratios adjusted for all other variables in table. All variables were fitted using the categorisation displayed in the table (i.e. age group as a 6-level non-ordered categorical variable).

b person-years/1,000

c per 1,000 person-years

Subsequent time refers to the time and rate after the procedure until the completion of follow-up.

Table 3: Rates of VTE by stage stratified by treatment

							Univariable			Multivariable[d]		
		Events	Time (1000s years)	Rate	95%	CI	HR	95%	CI	HR	95%	CI
No active therapy[a]	Local disease	160	29.99	5.3	4.6	6.2	Reference			Reference		
	Regional disease	113	14.94	7.6	6.3	9.1	1.4	1.1	1.8	1.4	1.1	1.8
	Distant metastases	18	1.03	17.5	11.0	27.7	3.2	2.0	5.2	2.5	1.6	4.2
	Unknown	170	22.67	7.5	6.5	8.7	1.4	1.1	1.8	1.2	1.0	1.6
Active chemotherapy[b]	Local disease	27	0.43	63.0	43.2	91.9	Reference			Reference		
	Regional disease	38	0.74	51.3	37.3	70.5	0.8	0.5	1.3	0.8	0.5	1.2
	Distant metastases	*	*	26.2	6.6	104.8	0.4	0.1	1.7	0.3	0.1	1.4
	Unknown	30	0.46	65.7	45.9	93.9	1.1	0.6	1.8	1.0	0.6	1.7
Active surgery[c]	Local disease	26	0.92	28.1	19.2	41.3	Reference			Reference		
	Regional disease	9	0.52	17.2	8.9	33.0	0.6	0.3	1.3	0.6	0.3	1.4
	Distant metastases	*	*	24.2	3.4	171.5	0.9	0.1	6.4	0.8	0.1	5.7
	Unknown	14	0.65	21.5	12.7	36.3	0.8	0.4	1.5	0.7	0.4	1.4

a Cohort time where participants are not at risk due to surgery or chemotherapy

b During chemotherapy and for the 2 months following completion of therapy. Excludes person-time where participants are at risk following surgery.

c During surgery and for the first 2 months following discharge from the surgical hospital admission. Excludes person-time where participants are at risk during or following chemotherapy.

d Adjusted for grade, endocrine therapy, BMI, comorbidity (Charlson) and age. These variables were fitted using the same categorisation as in multivariable models presented in Table 2.

* Number of outcome events and person-time are censored for cell frequencies <5 in line with CPRD policy

Table 4: Rates of VTE by surgery and chemotherapy

		Events	Person-years	Rate (per 1,000 pys)	95% CI	
Baseline [a]		450	67,600	6.7	6.1	7.3
Surgery only[b]	During surgery hospitalisation	*	*	12.2	3.1	48.9
	1st month following discharge	24	1,075	22.3	15.0	33.3
	2nd month following discharge	24	893	26.9	18.0	40.1
	3rd month following discharge	8	818	9.8	4.9	19.6
Chemotherapy only[c]	During chemotherapy	75	1,080	69.4	55.4	87.1
	1 month after chemotherapy	13	271	48.0	27.9	82.6
	2 months after chemotherapy	5	224	22.3	9.3	53.7
	3 months after chemotherapy	*	*	14.6	4.7	45.3
Surgery and chemotherapy	Chemotherapy during surgery recovery	*	*	9.4	2.4	37.6
	Surgery[d] during chemotherapy recovery	5	54	92.1	38.3	221.2

a Includes all cohort time aside for the time during (and 3 months following) chemotherapy and during the surgical hospital admission and 3 months following discharge. This includes the entire study time for women who did not undergo either chemotherapy or surgery.
b Excludes time during (and 3 months following) chemotherapy
c Excludes time whilst hospitalised for surgery and 3 months following discharge
d Includes time during surgical admission and the 3 months following discharge
* Number of outcome events and person-time are censored for cell frequencies <5 in line with CPRD policy

Table 5: Rates of VTE by type of endocrine therapy

	Events	Person-years	Rate per 1,000 person-years	95%	CI	Univariable Cox model HR	95%	CI	Multivariable Cox model[e] HR	95%	CI
Tamoxifen only (n=5,415)											
Before therapy	7	1,198	5.8	2.8	12.3		Reference			Reference	
First 3 months[a]	30	1,246	24.1	16.8	34.4	4.1	1.8	9.4	5.5	2.3	12.7
Subsequent time	159	30,453	5.2	4.5	6.1	1.1	0.5	2.9	1.9	0.9	4.3
Aromatase inhibitors only (n=1,410)											
Before therapy	28	627	44.6	30.8	64.7		Reference			Reference	
First 3 months[a]	9	318	28.3	14.7	54.3	0.6	0.3	1.3	0.8	0.5	1.4
Subsequent time	46	4,697	9.8	7.3	13.1	0.2	0.1	0.4	0.3	0.2	0.5
Tamoxifen followed by AIs (n=3,821)[d]											
Before Tamoxifen	18	1,121	16.1	10.1	25.5		Reference			Reference	
First 3 months of Tamoxifen[b]	29	859	33.8	23.5	48.6	2.1	1.2	3.8	2.3	1.2	4.4
Subsequent time for Tamoxifen[b]	97	8,812	11.0	9.0	13.4	0.7	0.4	1.1	1.1	0.6	2.0
First 3 months of AIs	10	852	11.7	6.3	21.8	0.7	0.3	1.6	1.0	0.4	2.4
Subsequent time for AIs[c]	78	11,509	6.8	5.4	8.5	0.4	0.2	0.7	0.6	0.3	1.2

a 3 months from day of the first Tamoxifen/AI prescription following cancer diagnosis

b Exposure period ceases on the day in which patients switch to AI (if applicable)

c Cohort time starting 3 months after commencing AIs until the completion of follow-up

d An equivalent analysis was not presented for the 233 women (12 VTE events) who switched from AIs to Tamoxifen as this number was too small for a meaningful analysis.

e Adjusted for stage, grade, surgery, chemotherapy, BMI, comorbidity (Charlson) and age. These variables were fitted using the same categorisation as in multivariable models presented in Table 2.

Figure 1: Rates of VTE around chemotherapy