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## **Chemotherapy, genetic susceptibility and risk of venous thromboembolism in breast cancer patients.**

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## **Translational relevance**

Venous thromboembolism (VTE) is a serious complication in breast cancer patients, and many events occur during chemotherapy. Routine thromboprophylaxis, however, is not recommended in chemotherapy-treated patients due the increased risk of bleeding. Since VTE is highly heritable, genetic markers are promising candidates for the identification of high-risk patients who could potentially benefit from thromboprophylactic measures. In this study, we report VTE risks by chemotherapy and genetic susceptibility in a population-based cohort of 4261 breast cancer patients. Chemotherapy and genetic susceptibility independently influenced VTE risk, with a 1-year cumulative incidence of 9.5% in patients carrying both risk factors. A statistical interaction between genetic susceptibility and age was found, resulting in an excess VTE risk (1-year cumulative incidence = 25.0%) in those aged  $\geq 60$  years. Our study demonstrates the potential of genetic testing for VTE risk stratification in the chemotherapy setting, which seems to be most informative in older patients.

## **Abstract**

Purpose: Venous thromboembolism (VTE) is highly heritable and a serious complication of cancer and its treatment. We examined the individual and joint effects of chemotherapy and genetic susceptibility on VTE risk in breast cancer patients.

Experimental design: A Swedish population-based study including 4,261 women diagnosed with primary invasive breast cancer between 2001 and 2008 in Stockholm, followed until 2012. Risk stratification by chemotherapy and genetic susceptibility [a polygenic risk score (PRS) including 9 established VTE loci] was assessed using Kaplan-Meier and flexible parametric survival analyses, adjusting for patient, tumor and treatment characteristics.

Results: In total, 276 patients experienced a VTE event during a median follow-up of 7.6 years. Patients receiving chemotherapy [HR (95% CI) = 1.98; 1.40-2.80] and patients in the highest 5% of the PRS [HR (95% CI) = 1.90; 1.24-2.91] were at increased risk of developing VTE. Chemotherapy and PRS acted independently on VTE risk and the 1-year cumulative incidence in patients carrying both risk factors was 9.5% compared to 1.3% in patients not having these risk factors ( $P < 0.001$ ). Stratified analyses by age showed that the risk-increasing effect of PRS was stronger in older patients ( $P$  interaction = 0.04), resulting in an excess risk among genetically susceptible patients receiving chemotherapy aged  $\geq 60$  years (1-year cumulative incidence = 25.0%)

Conclusions: Risk stratification by chemotherapy and genetic susceptibility identifies breast cancer patients at high VTE risk, who could potentially benefit from thromboprophylaxis. Our results further suggest that genetic testing is more informative in older breast cancer patients.

## Introduction

Venous thromboembolism (VTE) is a serious complication in breast cancer patients, resulting in significant morbidity, mortality, and health-care associated costs (1-3). The incidence of VTE is relatively low in breast cancer patients (~1-2%) (1, 4) compared to other cancer populations (up to ~8% in pancreatic cancer) (4, 5), but as one of the most common cancers, breast cancer contributes to a large number of cancer-associated VTE cases. Long-term consequences of VTE in terms of future complications (2) and quality of life (6) are substantial, especially for non-metastatic patients who have a rather good prognosis.

The incidence of VTE varies considerably among breast cancer patients and is particularly high shortly after diagnosis during chemotherapy treatment (5, 7-9). Routine thromboprophylaxis is not recommended in patients receiving chemotherapy, but expert consensus statements encourage an individualized approach to identify high-risk patients who could potentially benefit from thromboprophylactic measures (10, 11).

In addition to chemotherapy, hereditary factors strongly contribute to VTE risk. The heritability of VTE has been estimated at 50-60% (12, 13) and 9 susceptibility loci have been identified to date (14), of which rs6025 [called Factor V Leiden (FVL)] is the most established, accounting for ~20% of all VTE cases (15). Measures of genetic susceptibility including FVL carriership (16, 17) and VTE family history (18) have been associated with a ~2-fold increased risk of VTE in cancer patients, and several lines of evidence suggest that genetic markers are promising candidates for further risk stratification of high-risk patients (16-18). Few studies, however, have evaluated the excess risk associated with genetic susceptibility in chemotherapy-treated patients. A case-control study (19) found an increased risk of thrombosis during chemotherapy in breast cancer patients carrying the FVL mutation whereas no risk-increasing effect of FVL was observed in a small prospective study (20). No

studies to date have examined the collective impact of multiple genetic loci and little is known about potential age-dependent effects in breast cancer patients, although previous reports suggest a stronger impact of FVL with advancing age (21, 22).

In the present study, we assessed the individual and joint effects of chemotherapy and genetic susceptibility on VTE risk, overall and by age at diagnosis. Genetic effects were evaluated using a polygenic risk score (PRS) incorporating known VTE risk loci.

## **Methods**

### Study population

For the present study, we analyzed patients from the Libro-1 study, a prospective cohort study aimed at identifying risk and prognostic factors for breast cancer (23, 24). The Libro-1 study comprises women diagnosed with primary invasive breast cancer between 2001 and 2008 in the Stockholm-Gotland region, who were invited for questionnaire interviews and blood sampling in 2009. All patients were identified through the Stockholm Breast Cancer Register, which has high completeness (99%) and includes detailed information on tumor characteristics and breast cancer treatment (25). In total, 4851 patients (63%) consented to participate of whom 4261 donated blood. All patients were diagnosed at age 25 to 75 years and had no distant metastases at diagnosis. The study population was linked by the unique personal identity number to the National Patient Register, Cause of Death Register, Population Register and Prescribed Drug register, and follow-up was complete until 31 December 2012. The study was approved by the Regional Ethical Review Board in Stockholm (Sweden) and all participants gave written informed consent.

### Venous thromboembolism

Venous thromboembolism events were identified through the Swedish Patient Register which has nationwide coverage since 1987 and includes all inpatient hospitalizations in Sweden (26). Since 2001, Swedish counties are also obliged to report hospital-based outpatient physician visits. VTE was defined according to the International Classification of Diseases (ICD) including diagnostic codes as described elsewhere (27, 28) (**Supplementary Table 1**). The validity of Swedish hospital discharge diagnoses for specific cardiovascular disorders, including VTE, is high and has been estimated to be around 90% (29). For sensitivity analyses, we used additional data from the Prescribed Drug Register which contains data on all drugs dispensed from Swedish pharmacies from July 2005 and onwards.

### Chemotherapy and other covariates

Information on chemotherapy administration was obtained from the Stockholm Breast Cancer Register. Patient characteristics, , tumor pathology and other treatment specifics were also extracted from this register, including age and menopausal status at diagnosis, tumor size, histological grade, number of affected lymph nodes, endocrine therapy, radiotherapy, and type of surgery. Information on VTE and comorbid disease prior to diagnosis was retrieved through the Swedish Patient Register. We selected all comorbid conditions relevant to VTE (28) including chronic obstructive pulmonary disease, obesity, alcoholism and alcohol-related liver disease, coronary heart disease, stroke, hypertension, sepsis, varicose veins, peripheral vascular disease and congestive heart failure. Pre-diagnostic information on smoking, physical activity, oral contraceptive use and hormone replacement therapy (HRT) was extracted from questionnaires. Participants were also asked to report their weight and height at study entry, from which BMI was calculated.

### VTE polygenic score

Blood-derived DNA samples were genotyped on the custom Illumina iSelect genotyping array (iCOGS) including 211,155 single nucleotide polymorphisms (SNPs) (30) with imputation to the 1000 Genomes Project March 2012 release as described previously (31). We selected all genome-wide significant SNPs ( $P \leq 5 \times 10^{-8}$ ,  $n = 9$ ) that were identified and replicated by a recent meta-analysis of genome-wide association studies (GWAS) (14) (**Supplementary Table 2**). All SNPs were imputed and passed quality control criteria for imputation:  $R^2 > 0.3$ , minor allele frequency  $\geq 0.01$ , and no deviation from Hardy-Weinberg equilibrium at  $P < 0.05$ . We constructed a weighted polygenic risk score (PRS) for each patient using the following formula:

$$\text{PRS} = \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n$$

where  $\beta$  is the per-allele log odds ratio (OR) for VTE associated with the risk allele for the  $k^{\text{th}}$  SNP ( $\text{SNP}_k$ ) and  $x_k$  is the number of alleles for  $\text{SNP}_k$  (0,1,2) and  $n = 9$  is the total number of SNPs. Literature-based effect sizes ( $\beta$ ) were derived from the GWAS meta-analysis (**Supplementary Table 2**) (14) and a log-additive model was used for PRS construction, since pairwise SNP-SNP interaction analyses did not show evidence of departure from this model. For comparison, we also analyzed associations with FVL carriership separately.

### Statistical analyses

We studied both individual and joint effects of chemotherapy and genetic susceptibility on VTE risk. The impact of genetic predisposition was analyzed using the PRS divided into percentile groups (< p25, p25-p75, p75-p95, > p95). For combined chemotherapy and genetic analyses, the PRS was dichotomized using the 95th percentile as a cutoff.



Relative risks of VTE were analyzed using Cox proportional hazards models and cumulative incidences were visualized using Kaplan-Meier plots. Numbers of person-years at risk were calculated from the date of breast cancer diagnosis until the date of first VTE event, emigration, death or end of the study period (December 31, 2012) whichever came first. We constructed four models to assess the impact of potential confounding factors: model 1 adjusting for age at diagnosis (years); model 2 adjusting for age at diagnosis (years) plus other patient characteristics [menopausal status (premenopausal vs. postmenopausal), VTE history (yes vs. no), BMI ( $< 25 \text{ kg/m}^2$ ,  $25\text{-}30 \text{ kg/m}^2$ ,  $> 30 \text{ kg/m}^2$ ), smoking (never, former, current), physical activity ( $< 1 \text{ hour/week}$ ,  $\geq 1 \text{ hour/week}$ ), oral contraceptive use (ever vs. never) and HRT (ever vs. never)]; model 3 with further adjustment for tumor characteristics [tumor size ( $\leq 10 \text{ mm}$ ,  $11\text{-}20 \text{ mm}$ ,  $21\text{-}30 \text{ mm}$ ,  $31\text{-}40 \text{ mm}$ ,  $> 40 \text{ mm}$ ), histological grade (low, moderate, high), number of affected lymph nodes (0, 1-4,  $> 4$ )]; and model 4 including all patient, tumor and treatment characteristics [endocrine therapy (yes vs. no), radiotherapy (yes vs. no) and type of surgery (partial vs. total mastectomy)].

Interactions on an additive scale were evaluated by comparing joint and individual effects, and multiplicative interactions were tested by adding a product term to the model. The proportional hazards assumption was verified using tests for Schoenfeld residuals and in case of non-proportionality, time-dependent effects were modelled using flexible parametric survival models (FPM) (32), as described in detail elsewhere (25).

We conducted four sensitivity analyses to test the robustness of our findings. First, we addressed potential misclassification of the outcome by re-analyzing all associations in patients diagnosed after July 2005 with available prescription data. To increase specificity of the outcome, 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. In a second sensitivity analysis, we checked whether results were

similar in patients with no VTE history. Third, we evaluated the impact of disease recurrence during follow-up on VTE risk. For this analysis, person-time was additionally censored at recurrent events (defined as distant metastasis, locoregional recurrence and diagnosis of a second primary cancer). Finally, due to our study design, analyses could in theory be subject to survivorship bias, since patients had to be alive in 2009. Although overall survival was high in the source population (92% of all patients diagnosed between 2001 and 2008 were alive and eligible for participation in Libro-1), we decided to carry out a third sensitivity analysis including patients diagnosed from January 2005 onward to address a theoretically possible bias.

## Results

Descriptive characteristics of the study population are summarized in **Table 1**. Additional information on patient, tumor and treatment characteristics can be found in **Supplementary Table 3**. Mean age at diagnosis was 58 years and 1648 (38.9%) patients received chemotherapy at diagnosis. In total, 276 patients experienced a VTE event during a median follow-up of 7.6 years (VTE rate = 8.6 per 1000 person-years; 95% CI = 7.0-9.7).

**Figure 1** shows the distribution of the risk alleles in the study population, stratified by incident VTE. As expected, the distribution was shifted towards higher values in patients who experienced a VTE event during follow-up. The weighted PRS based on all risk alleles showed a dose-response relation with VTE ( $P$  trend < 0.001) with patients in the highest 5% of the PRS having a significant increase in VTE risk compared to those in the middle PRS quintile.

**Table 2** lists the HRs for VTE according to chemotherapy and PRS, individually and combined. Overall, chemotherapy was associated with a ~2-fold increased risk of VTE (HR = 1.80; 95% CI = 1.40-2.31). The association was not materially different in multivariable

analyses adjusting for patient, tumor and treatment characteristics (HR = 1.98; 95% CI = 1.40-2.80). Also, no major differences in risk were observed for different chemotherapy agents and in stratified analyses by subsequent endocrine therapy (**Supplementary Table 4**). Time-dependent analyses showed evidence of non-proportional hazards, with the HR for chemotherapy only being increased within the first year of diagnosis (**Figure 2**).

Patients with a high genetic score (top 5% of PRS) had a 2-fold increased risk of VTE compared to patients having lower genetic scores (HR = 1.90; 95% CI = 1.24-2.91) (**Table 2**). The joint effect of chemotherapy and genetic susceptibility (HR = 3.84; 95% CI = 1.91-7.71) was not higher than expected based on the product of the individual effects. Stratified analyses by age showed that the PRS effect was stronger in patients aged  $\geq 60$  years (HR = 2.44; 95% CI = 1.37-4.35) than in those aged  $< 60$  years (HR = 1.31; 95% CI = 0.67-2.55,  $P$  interaction = 0.04).

**Figure 3** shows the cumulative incidence of VTE by different strata of chemotherapy and genetic susceptibility, overall and stratified by age at diagnosis. The 1-year cumulative incidence was similar for patients carrying only one of the two risk factors, i.e. 5.0% for chemotherapy-treated patients with a low genetic score ( $<$  top 5% of the PRS) and 4.3% for patients with a high genetic score not receiving chemotherapy. Combined, both risk factors resulted in a 1-year cumulative incidence of 9.5%. Stratified analyses by age showed a stronger risk-increasing effect of the PRS with advancing age, resulting in an excess VTE risk in older patients carrying both risk factors (1-year cumulative incidence = 25.0%).

FVL carriership was observed in 341 patients; 337 with a heterozygous genotype and 4 with a homozygous genotype. Substitution of the PRS by FVL carriership yielded similar results in terms of relative (**Supplementary Table 5**) and absolute VTE risks (**Supplementary Figure 1**).

Results of sensitivity analyses are summarized in **Supplementary Tables 6 and 7**.

Risk estimates were not materially different in analyses using a more stringent outcome definition; the slightly increased HRs for chemotherapy reflects the stronger risk increasing effect with shorter follow-up time. Also, exclusion of patients with a VTE history did not have a meaningful effect. Analyses with additional censoring at recurrent events showed no difference in VTE risk estimates, indicating that disease recurrence has no strong effect on VTE risk in the first 5 years following diagnosis. Sensitivity analyses further argue against a notable survivor bias, as relative and absolute risk estimates were similar when restricting the study population to more recently diagnosed cases.

## **Discussion**

Venous thromboembolism is a well-known complication in breast cancer patients, but studies focusing on risk stratification are scarce. To our knowledge, this is the first population-based study evaluating individual and joint effects of chemotherapy and genetic susceptibility on VTE risk by time since diagnosis. Our results confirm a strong independent effect of chemotherapy. The excess risk associated with chemotherapy was further increased by genetic susceptibility, with short-term absolute risks reaching clinical significance in patients with a high genetic score, defined as the top 5% of the PRS. Stratified analyses by age further showed that the risk-increasing effect of the PRS was stronger in older breast cancer patients.

The observed VTE incidence in chemotherapy-treated patients is comparable to previously reported chemotherapy effects in breast and other cancer populations (7-9). Several mechanisms have been proposed for the high thrombogenic potential of chemotherapy, including damage to the vascular endothelium, release of procoagulant factors after chemotherapy-induced apoptosis and use of intravascular devices for chemotherapy delivery (33, 34). Of note, the HR for chemotherapy was robust and remained unchanged after

adjustment for age, lifestyle factors, comorbidities, tumor size, grade, lymph node status and other treatment-related markers of disease aggressiveness. This result is consistent with clinical trial data supporting a strong independent effect of chemotherapy (9, 35). In agreement with previous reports (36, 37), the impact of chemotherapy was only detectable shortly after diagnosis during active treatment, making it an ideal candidate for thromboprophylaxis (38). This, in contrast to endocrine therapy for which no excess risk is seen immediately after diagnosis (39) and therefore a less optimal target for short-term prophylaxis. Clinical trial data show a lower VTE incidence with prophylactic anticoagulation in chemotherapy-treated cancer patients (40), but given the risk of bleeding, additional risk factors need to be considered for optimal prophylaxis (10, 11, 41).

In the present study, we demonstrate that a PRS based on a log-additive model of 9 SNPs, can be used for risk stratification of patients receiving chemotherapy. The HR for the top 5% of the PRS was similar in magnitude to the previously reported risk estimates for VTE family history (18) and FVL carriership (16, 17). Since the majority of patients in the highest 5% of the PRS were FVL carriers (93%), these results may suggest that a routinely available test is sufficient for identifying patients at highest risk. Indeed, relative and absolute risk estimates were similar for FVL carriership. However, an advantage of the PRS is that risks can be determined across a continuum allowing the identification of low, intermediate and high-risk patients. Moreover, previous reports have demonstrated increased discriminatory power with inclusion of multiple SNPs (42, 43) and with the ongoing discovery of novel risk loci this approach will ultimately provide more accurate predictions. We also found a statistical interaction with age, suggesting the genetic impact to be stronger in older breast cancer patients. Although the *P* value for interaction (0.04) was not strongly significant, and we cannot rule out the possibility of an effect being missed in younger patients due to small

numbers of events, this result is consistent with the previously observed interaction between FVL and age on VTE risk (21, 22). While the impact of genetic susceptibility is generally more profound in younger individuals, stronger effects of genetic loci with increasing age do exist, and have been reported for other traits (44, 45). The observed interaction can be interpreted in light of the multifactorial etiology of VTE requiring interactions between inherited and acquired risk factors. Since the vascular environment changes with age (i.e. increased vascular stiffness in older individuals), a stronger genetic effect at older age is considered plausible (21, 45). Similarly, accumulation of lifestyle and environmental exposures may trigger epigenetic mechanisms, resulting in changes in gene expression with aging (45). Regardless of the mechanism involved, this finding suggests that a patient's age is an important parameter when considering genetic testing in breast cancer patients, that requires evaluation in future risk stratification efforts.

Several other factors have been proposed for the identification of high-risk cancer patients receiving chemotherapy. The Khorana risk model including 5 clinical and laboratory measures (primary cancer site, pre-chemotherapy platelet count, hemoglobin level and/or use of erythropoiesis-stimulating agents, leukocyte count and BMI) is the most established one (46). This model, however, does not incorporate genetic data and is not specific for breast cancer patients. In contrast to other biomarkers which are influenced by acute inflammation, surgery and clinical stage, genetic factors do not require repeated measurement as they are fixed and independent of disease state and/or intervention. Of note, the short-term VTE risk in chemotherapy-treated patients with a high-genetic score is within the range of previously reported risks in high-risk cancer patients according to the Khorana-model (6.8-17.9%) (47). These absolute risks are also comparable with risks observed in hospitalized and postoperative patients for whom routine prophylaxis has been shown effective (48) and is

recommended by international guidelines (49, 50). Further studies, however, are needed to investigate the joint effect of genetic markers and other clinical risk factors in VTE risk prediction, and to identify specific high-risk patients in which thromboprophylaxis is considered beneficial and safe.

The main strength of our study is the population-based design and linkage to register-based data which minimizes information bias. Other strengths include the detailed information on patient, tumor and treatment characteristics, and the use of flexible parametric models for analyzing time-varying effects. Previous studies evaluating risk stratification by genetic factors were either small (20) or limited by case-control design (19), from which no absolute risks could be inferred. Compared to older registry-based studies (1, 4), our study further benefited from the inclusion of in- and outpatient VTE diagnoses, with absolute risk estimates (overall and by chemotherapy) corresponding to those observed in a recent UK study using similar diagnostic codes (39). There are also several methodological aspects that need to be mentioned. First, analyses were based on registry-based VTE diagnoses and despite their high validity some misclassification may have occurred. Risk estimates were, however, not materially different in sensitivity analyses using a more stringent definition, and the impact of potential misclassification was further reduced by analyzing main diagnoses only. Second, outpatient VTE diagnoses were only registered from 2001 onward, which might have led to an underestimation of prevalent VTE cases. Analyses excluding patients with a VTE history yielded similar results though. Third, participants of the Libro-1 study had to be alive in 2009. However, overall survival is high in non-metastatic patients and results were similar in sensitivity analyses including more recently diagnosed patients. Finally, SNPs were not directly genotyped, but imputed instead. The average information score for imputation (0.80)

was nevertheless high, and imperfectly measured genotypes could only have resulted in attenuated associations rather than producing spurious ones.

Collectively, our findings illustrate the potential of genetic testing for identifying breast cancer patients at high-risk of developing VTE following chemotherapy. Further research is needed to test the implementation of genetic information in VTE risk stratification of high-risk patients. Our data also suggest that the joint effect of chemotherapy and genetic susceptibility is particularly pronounced in older patients, an observation that warrants clinical attention.



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## **Authorship contributions**

Contribution: J.S.B. designed the research, analysed and interpreted the data and wrote the manuscript. E.H. designed the research, interpreted the data and contributed to the manuscript. K.H. and A.L.V.J. directed the statistical analyses, interpreted the data and contributed to the manuscript. J.F., J.B. and P.H. contributed to the research design, interpreted the data and contributed to the manuscript. K.C. designed the research, collected and interpreted the data and contributed to the manuscript.

## **Disclosure of Conflicts of Interest**

None of the authors have conflicts of interests to declare.

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## Figure legends

**Figure 1.** Distribution of VTE risk allele count and hazard ratios for venous thromboembolism by PRS percentile group.

A = Distribution of risk allele count, stratified by incident VTE. B = hazard ratios for VTE by PRS percentile groups (middle quintile is reference group). Abbreviations: VTE = venous thromboembolism; HR = hazard ratio; CI = confidence interval; PRS = polygenic risk score.

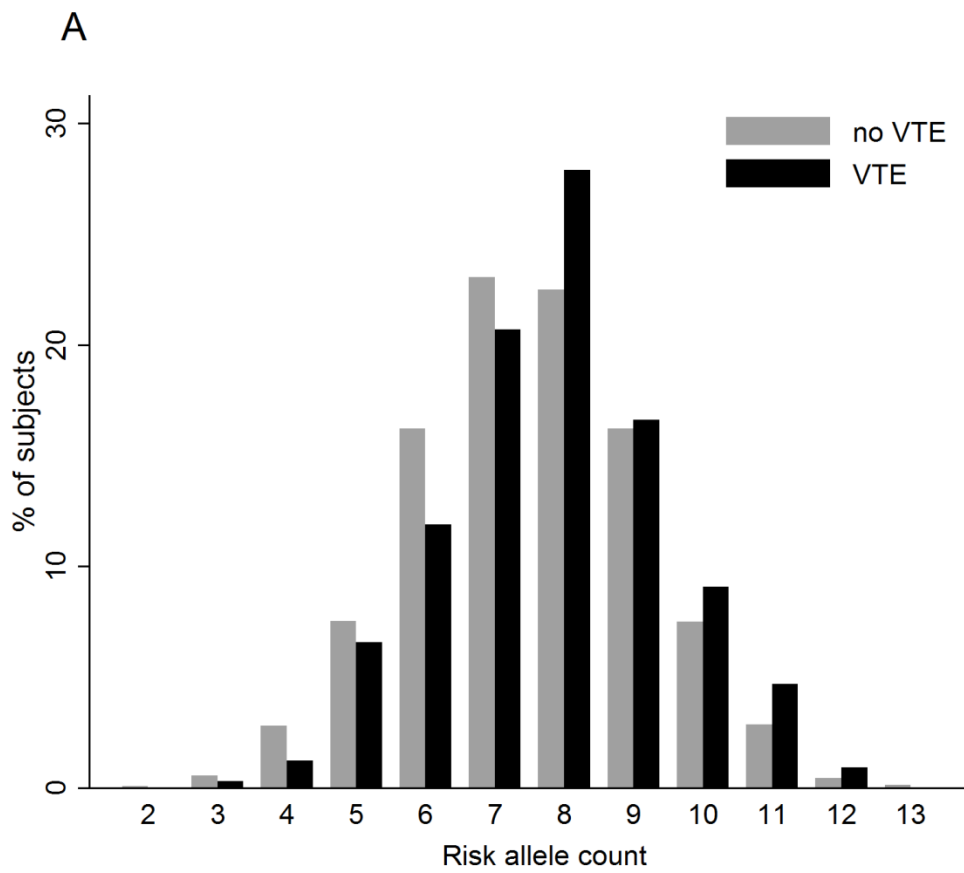
**Figure 2.** Time-dependent effect of chemotherapy on venous thromboembolism risk in breast cancer patients.

Time-dependent hazard ratios for chemotherapy (yes vs. no). Hazard ratios are multivariable adjusted (model 4) and estimated from a flexible parametric survival model with time since diagnosis as underlying time scale.

**Figure 3.** Cumulative incidence of venous thromboembolism in breast cancer patients by chemotherapy and genetic susceptibility, overall and stratified by age at diagnosis.

Abbreviations; PRS = polygenic risk score. Cumulative incidence of VTE by strata of chemotherapy and PRS (top 5%): all patients (A), patients aged < 60 years (B), patients aged  $\geq 60$  years (C). All estimates are obtained from Kaplan-Meier analysis with time since diagnosis as underlying time scale. Log-rank test  $P$  values:  $P < 0.001$  (A);  $P = 0.001$  (B),  $P < 0.001$  (C).

Figure 1



B

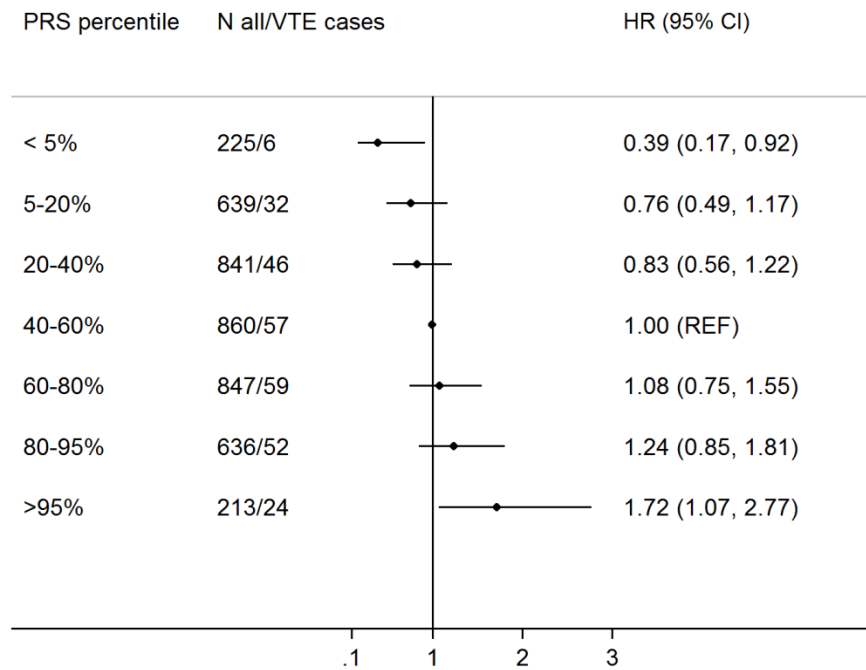


Figure 2

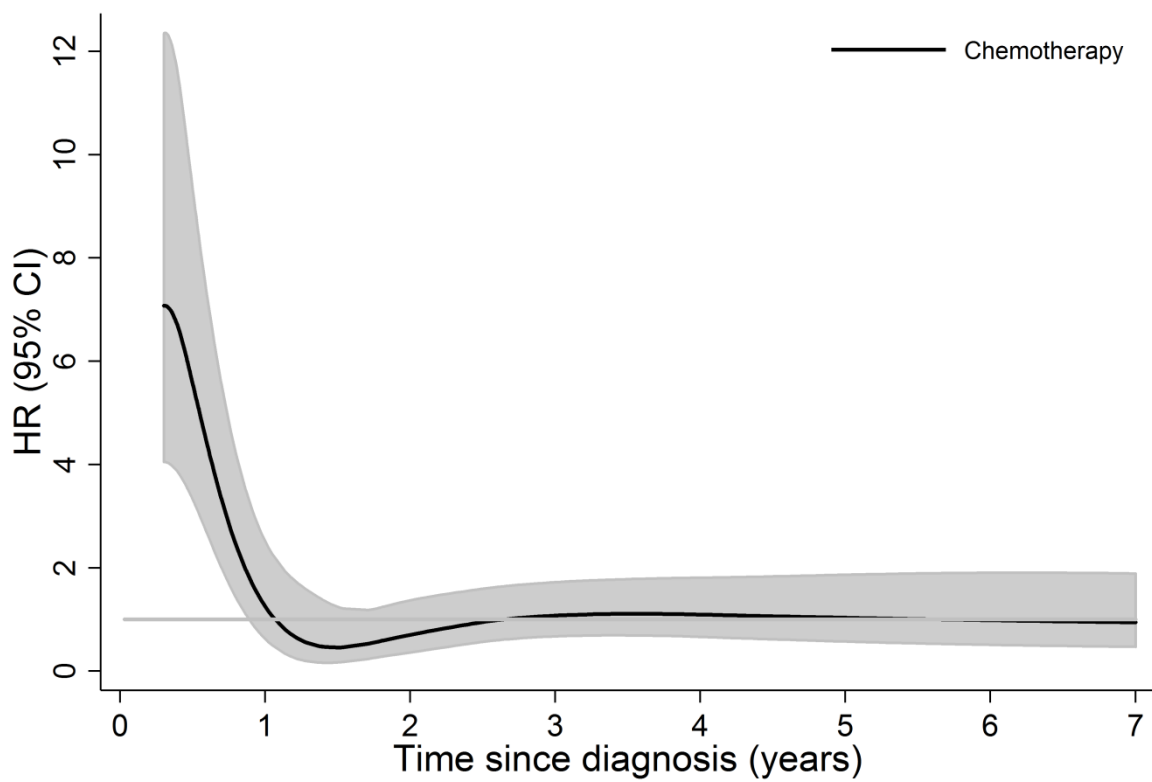
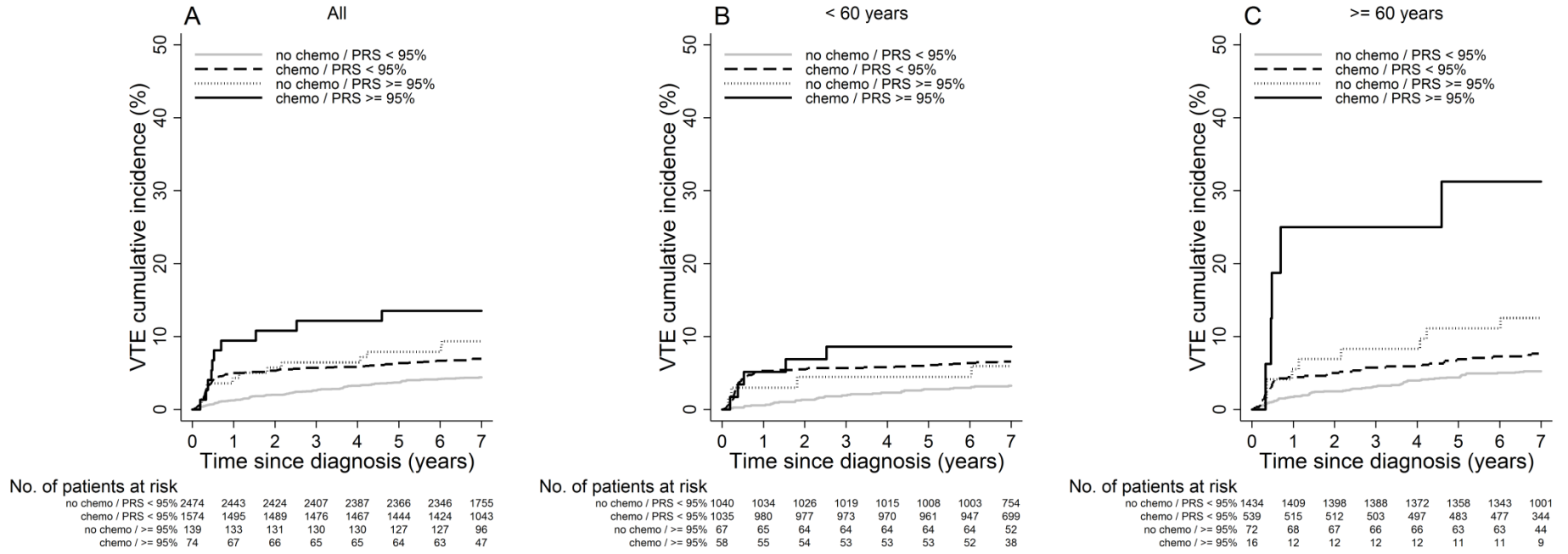


Figure 3



**Table 1.** Characteristics of the study population.

<b>Characteristics</b>	<b>Stockholm breast cancer cohort (N = 4261)</b>
Age at diagnosis (years)	
mean (SD)	58.1 (9.5)
Year of diagnosis	
2001-2004	47.6 (2031)
2005-2008	52.3 (2230)
Menopausal status, % (N)	
Premenopausal	23,8 (1014)
Postmenopausal	69,9 (2982)
Missing	6,2 (265)
VTE history, % (N)	
No	97,9 (4171)
Yes	2.1 (90)
Chemotherapy, % (N)	
No	61.3 (2613)
Yes	38.7 (1648)
Endocrine therapy, % (N)	
No	16.2 (692)
Yes	83.8 (3569)
PRS	
Mean (SD)	0.10 (0.03)
Min-Max	0.02-0.27
Factor V Leiden, % (N)	
Non-carrier	92.0 (3920)
Carrier	8.0 (341)

Abbreviations: CI = confidence interval; SD = standard deviation; PRS = polygenic risk score; VTE = venous thromboembolism.

**Table 2.** Venous thromboembolism risk in breast cancer patients by chemotherapy and genetic susceptibility.

	N all/VTE cases	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
<b>Chemotherapy</b>					
No	2613/144	REF	REF	REF	REF
Yes	1648/132	1.80 (1.40-2.31)	1.81 (1.41-2.33)	1.83 (1.32-2.54)	1.98 (1.40-2.80)
<b>PRS (percentiles)</b>					
< 95%	4048/252	REF	REF	REF	REF
≥ 95%	213/24	1.91 (1.25-2.90)	1.88 (1.23-2.87)	1.84 (1.20-2.82)	1.90 (1.24-2.91)
<b>Chemotherapy/PRS (percentiles)</b>					
no chemo / PRS < 95%	2474/130	REF	REF	REF	REF
chemo / PRS < 95%	1574/122	1.83 (1.41-2.36)	1.81 (1.40-2.34)	1.85 (1.32-2.59)	1.98 (1.39-2.82)
no chemo / PRS ≥ 95%	139/14	1.97 (1.14-3.42)	1.91 (1.09-3.34)	1.88 (1.07-3.30)	1.87 (1.06-3.28)
chemo / PRS ≥ 95%	74/10	3.71 (1.93-7.14)	3.68 (1.90-7.10)	3.58 (1.79-7.16)	3.84 (1.91-7.71)

Abbreviations: HR = hazard ratio; CI = confidence interval; PRS = polygenic risk score; VTE = venous thromboembolism.

Model 1: model adjusted for age at diagnosis

Model 2: model 1 plus patient characteristics (menopausal status, VTE history, comorbidities, body mass index, smoking, physical activity, oral contraceptive use and hormone replacement therapy)

Model 3: model 2 plus tumor characteristics (tumor size, histological grade, number of affected lymph nodes)

Model 4: model 3 plus treatment characteristics (endocrine therapy, radiotherapy and surgery)