Clinical Cancer Research

Chemotherapy, Genetic Susceptibility, and Risk of Venous Thromboembolism in Breast Cancer Patients

Judith S. Brand[1], Elham Hedayati[2], Keith Humphreys[1], Jonas F. Ludvigsson[1,3], Anna L.V. Johansson[1], Jonas Bergh[2], Per Hall[1], and Kamila Czene[1]

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 patients with breast cancer.

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 nine 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 with 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 ≥ 60 years (1-year cumulative incidence = 25.0%).

Conclusions: Risk stratification by chemotherapy and genetic susceptibility identifies patients with breast cancer at high VTE risk, who could potentially benefit from thromboprophylaxis. Our results further suggest that genetic testing is more informative in older patients with breast cancer. *Clin Cancer Res; 22(21); 5249–55.* *©2016 AACR.*

Introduction

Venous thromboembolism (VTE) is a serious complication in patients with breast cancer, resulting in significant morbidity, mortality, and health-care–associated costs (1–3). The incidence of VTE is relatively low in patients with breast cancer (~1%–2%; refs. 1, 4) compared with other cancer populations (up to ~8% in pancreatic cancer; refs. 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 nonmetastatic 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% to 60% (12, 13), and nine 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 ~twofold increased risk of VTE in patients with cancer, 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 patients treated with chemotherapy. A case–control study (19) found an increased risk of thrombosis during chemotherapy in patients with breast cancer 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 patients with breast cancer, 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,

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [2]Department of Oncology-Pathology, Radiumhemmet, Karolinska Institutet and Karolinska University Hospital, Cancer Centre Karolinska, Stockholm, Sweden. [3]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden.

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Corresponding Author: Judith S. Brand, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels Väg 12A, 171 77 Stockholm, Sweden. Phone: 46-8-524-82352; Fax: 46-8-31 49 75; E-mail: judith.brand@ki.se

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Translational Relevance

Venous thromboembolism (VTE) is a serious complication in patients with breast cancer, frequently associated with chemotherapy. Routine thromboprophylaxis, however, is not recommended in patients treated with chemotherapy due to the increased risk of bleeding. Because 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 4,261 patients with breast cancer. 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 60 years and older. Our results suggest that genetic testing may have clinical potential for VTE risk stratification in the chemotherapy setting, particularly in older patients with breast cancer.

and by age at diagnosis. Genetic effects were evaluated using a polygenic risk score (PRS) incorporating known VTE risk loci.

Materials and Methods

Study population

For the present study, we analyzed patients from the Libro-1 study, a 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, 4,851 patients (63%) consented to participate, of whom 4,261 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

VTE 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 (refs. 27, 28; Supplementary Table S1). 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 onward.

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; ref. 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; ref. 14; Supplementary Table S2). All SNPs were imputed and passed quality control criteria for imputation: $R^2 > 0.3$, minor allele frequency ≥ 0.01, and no deviation from Hardy–Weinberg equilibrium at $P < 0.05$. We constructed a weighted PRS for each patient using the following formula:

$$\mathrm{PRS} = \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n$$

where β is the per-allele log odds ratio (OR) for VTE associated with the risk allele for the kth SNP (SNP_k), x_k is the number of alleles for SNP_k (0,1,2), and $n = 9$ is the total number of SNPs. Literature-based effect sizes (β) were derived from the GWAS meta-analysis (Supplementary Table S2; ref. 14), and a log-additive model was used for PRS construction, because 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 (<p5,p5-p20,p20-p40,p40-p60,p60-p80,p80-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 kg/m^2, 25–30 kg/m^2, >30 kg/m^2), smoking (ever vs. never), physical activity (<1 hour/week vs. $\geq$ 1 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 mm, 11–20 mm, 21–30 mm, 31–40 mm, >40 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 nonproportionality, time-dependent effects were modelled using flexible parametric survival models (FPM; ref. 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, because 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 S3. Mean age at diagnosis was 58 years, and 1648 (38.7%) 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 1,000 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 toward 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 with those in the middle PRS quintile.

Table 1. Characteristics of the study population

Characteristics	Stockholm breast cancer cohort (N = 4,261)
Age at diagnosis (y)	
mean (SD)	58.1 (9.5)
Year of diagnosis, % (N)	
2001–2004	47.7 (2,031)
2005–2008	52.3 (2,230)
Menopausal status, % (N)	
Premenopausal	23.8 (1,014)
Postmenopausal	70.0 (2,982)
Missing	6.2 (265)
VTE history, % (N)	
No	97.9 (4,171)
Yes	2.1 (90)
Chemotherapy, % (N)	
No	61.3 (2,613)
Yes	38.7 (1,648)
Endocrine therapy, % (N)	
No	16.2 (692)
Yes	83.8 (3,569)
PRS	
Mean (SD)	0.10 (0.03)
Min–max	0.02–0.27
Factor V Leiden, % (N)	
Non-carrier	92.0 (3,920)
Carrier	8.0 (341)

Table 2 lists the HRs for VTE according to chemotherapy and PRS, individually and combined. Overall, chemotherapy was associated with a ~twofold 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 S4). Time-dependent analyses showed evidence of nonproportional hazards, with the HR for chemotherapy only being increased within the first year of diagnosis (Fig. 2).

Patients with a high genetic score (top 5% of PRS) had a twofold increased risk of VTE compared with 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 60 years and older (HR = 2.44; 95% CI = 1.37–4.35) than in those aged less than 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%).

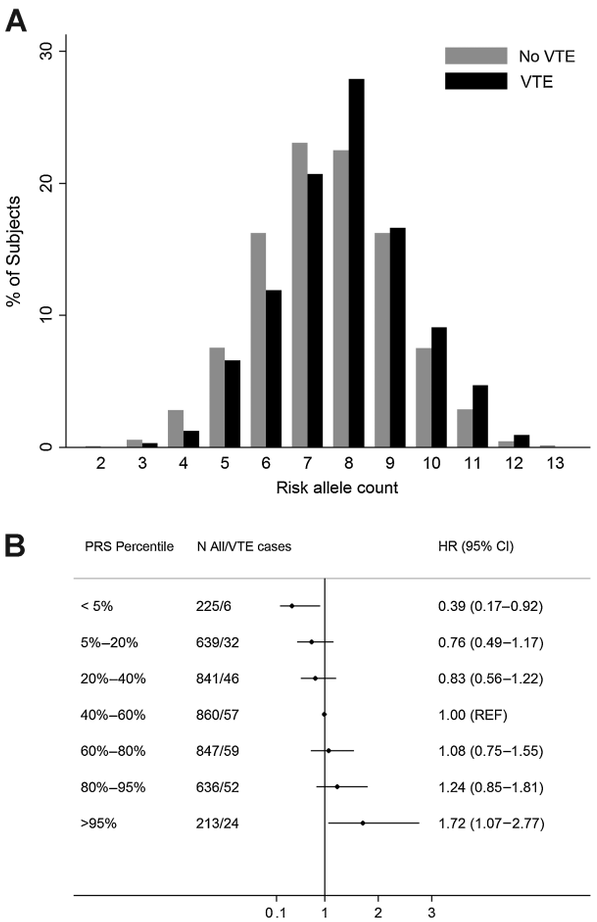

Figure 1.
Distribution of VTE risk allele count and hazard ratios for VTE by PRS percentile group. **A,** distribution of risk allele count, stratified by incident VTE. **B,** hazard ratios for VTE by PRS percentile groups (middle quintile is the reference group).

FVL carriership was observed in 341 patients: 337 with a heterozygous genotype and four with a homozygous genotype. Substitution of the PRS by FVL carriership yielded similar results

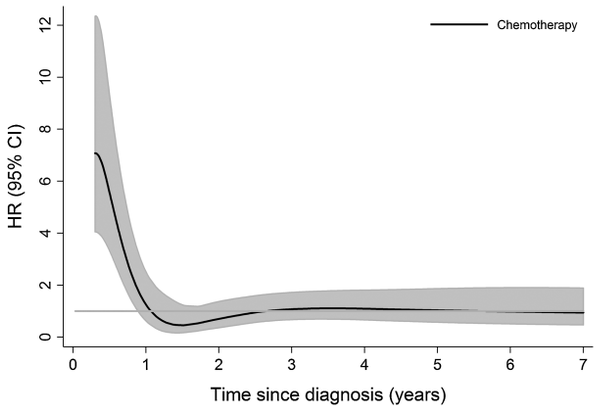

Figure 2.
Time-dependent effect of chemotherapy on VTE risk in patients with breast cancer. Time-dependent hazard ratios for chemotherapy (yes vs. no). Hazard ratios are multivariable adjusted (model 4) and estimated from a flexible parametric survival model with time since diagnosis as underlying time scale.

in terms of relative (Supplementary Table S5) and absolute VTE risks (Supplementary Fig. S1).

Results of sensitivity analyses are summarized in Supplementary Tables S6 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

VTE is a well-known complication in patients with breast cancer, 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

Table 2. VTE risk in patients with breast cancer by chemotherapy and genetic susceptibility

		HR (95% CI)			
	N all/VTE cases	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Chemotherapy					
No	2,613/144	REF	REF	REF	REF
Yes	1,648/132	1.80 (1.40–2.31)	1.81 (1.41–2.33)	1.83 (1.32–2.54)	1.98 (1.40–2.80)
PRS (percentiles)					
<95%	4,048/252	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)
Chemotherapy/PRS (percentiles)					
No chemo/PRS < 95%	2,474/130	REF	REF	REF	REF
Chemo/PRS < 95%	1,574/122	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)

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).

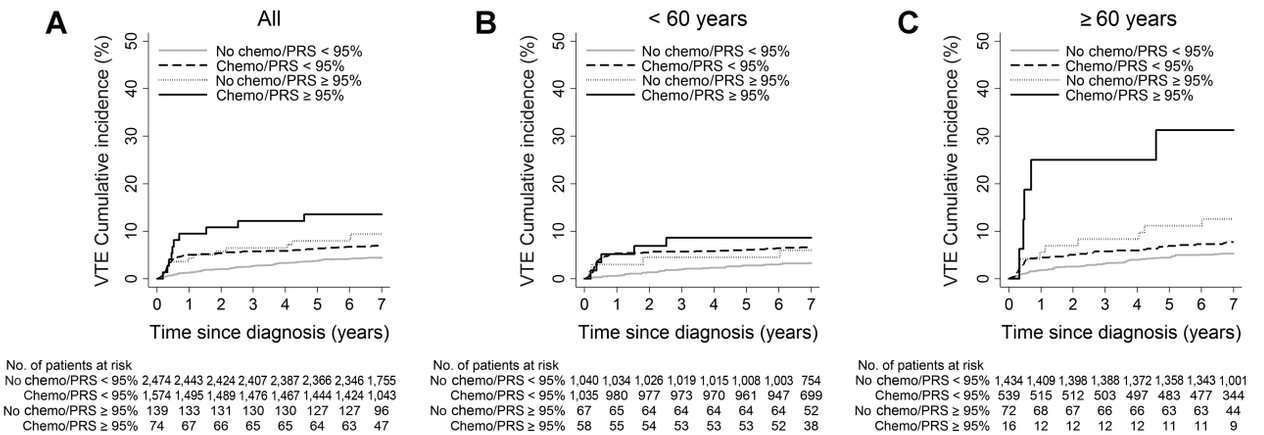

Figure 3.

Cumulative incidence of VTE in patients with breast cancer by chemotherapy and genetic susceptibility, overall and stratified by age at diagnosis. Cumulative incidence of VTE by strata of chemotherapy and PRS (top 5%): all patients (**A**), patients ages < 60 years (**B**), patients ages ≥ 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**).

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 patients treated with chemotherapy is comparable with 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 is in contrast to endocrine therapy for which no excess risk is seen immediately after diagnosis (39) and therefore a less ideal target for short-term prophylaxis. Clinical trial data show a lower VTE incidence with prophylactic anticoagulation in cancer patients treated with chemotherapy (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 nine 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). Because 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 patients with breast cancer. 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). Although 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. Because 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 patients with breast cancer, which 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 five 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 patients with breast cancer. In contrast to other biomarkers that 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 patients treated with chemotherapy who have a high-genetic score is within the range of previously reported risks in high-risk patients with cancer according to the Khorana model (6.8%–17.9%; ref. 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 with older registry-based studies (1, 4), our study further benefited from the inclusion of inpatient 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 nonmetastatic 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 patients with breast cancer 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funding resources had no role in the study design, data collection, analyses, data interpretation, writing the manuscript, or in the decision to submit the manuscript for publication.

Authors' Contributions

Conception and design: J.S. Brand, A.L.V. Johansson, K. Czene
Development of methodology: J.S. Brand, E. Hedayati, A.L.V. Johansson, J. Bergh, P. Hall, K. Czene
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Hall, K. Czene
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Brand, E. Hedayati, K. Humphreys, A.L.V. Johansson, J. Bergh, P. Hall, K. Czene
Writing, review, and/or revision of the manuscript: J.S. Brand, E. Hedayati, K. Humphreys, J.F. Ludvigsson, A.L.V. Johansson, J. Bergh, K. Czene
Study supervision: E. Hedayati, K. Czene

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