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

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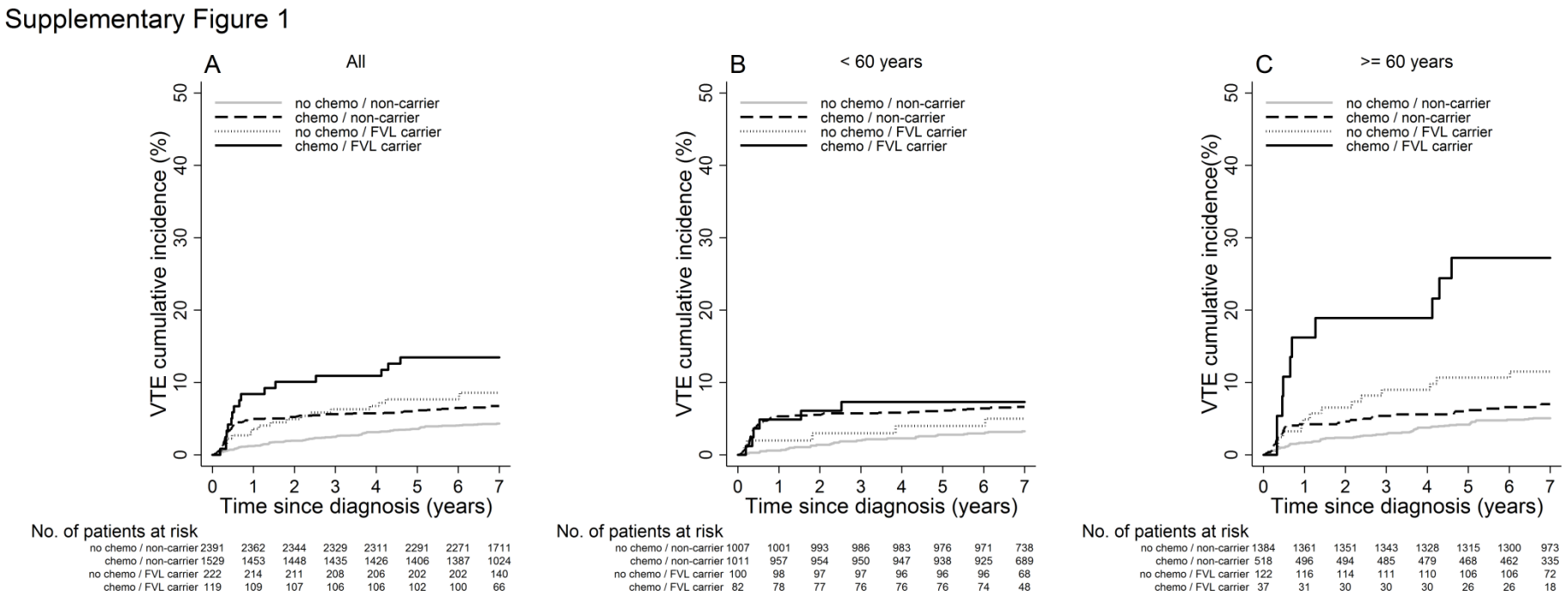
Supplementary Figure 1. Cumulative incidence of VTE by chemotherapy and FVL carriership, overall and stratified by age at diagnosis.



Abbreviations; FVL = Factor V Leiden. Cumulative incidence of VTE by strata of chemotherapy and FVL carriership: all patients (A), patients aged < 60 years (B), patients aged ≥ 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).

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Supplementary Table 1. ICD codes for venous thromboembolism (VTE).

	ICD-9	ICD-10
VTE		
Venous thrombosis of the legs	451,671C, 671D, 671E, 671X	I80, O222, O223, O229, O870, O871, O879, O087
Pulmonary embolism	415B, 416W, 673C, 639G	I26, O882,O082
Other forms of venous thromboembolism	452, 453, 437G, 671F	I81, I82, I636, I676, O225, O873

Abbreviations: VTE = venous thromboembolism; ICD = International Coding of Disease classification. ICD codes for venous thromboembolism according to the definition of Zöller et al.[26-28] . Only primary VTE diagnoses were considered for analyses.

Supplementary Table 2. Single nucleotide polymorphisms included in the VTE polygenic risk score (PRS).

CHR	SNP	Gene	Description	Alleles [a]	Risk allele frequency [b]	Allelic OR [c]	INFO-score [d]
1	rs4524	F5	Missense	C/T	0.74	1.20 (1.14-1.26)	0.94
1	rs6025	F5	Missense	C/T	0.04	3.25 (2.91-3.64)	0.85
4	rs2066865	FGG	3'UTR	G/A	0.28	1.24 (1.18-1.31)	0.60
4	rs4253417	F11	Intronic	T/C	0.40	1.27 (1.22-1.34)	0.88
9	rs529565	ABO	Intronic	T/C	0.40	1.55 (1.48-1.63)	0.99
10	rs78707713	TSPAN15	Intronic	C/T	0.86	1.28 (1.19-1.39)	0.96
11	rs1799963	F2	Intronic	G/A	0.01	2.29 (1.75-2.99)	0.49
19	rs2288904	SLC44A2	Missense	A/G	0.79	1.19 (1.12-1.26)	0.67
20	rs6087685	PROCR	Intronic	G/C	0.31	1.15 (1.10-1.21)	0.81

Abbreviations: CHR = chromosome; SNP = single nucleotide polymorphism; OR = odds ratio.[a] Alleles: reference allele / risk allele. [b] Risk allele frequency as observed in the study population. [c] Allelic OR: odds ratio per risk allele increase as derived from the GWAS meta-analysis by Germain et al [13]. [d] Information score for imputation; 1.00 corresponds to a genotyped variant.

Supplementary Table 3. Patient, tumor and treatment characteristics of the study population.

Characteristic	Stockholm breast cancer cohort (N = 4261)
Patient characteristics	
Comorbidities, % (N)	
No	90.9 (3875)
Yes	9.1 (386)
Body mass index, % (N)	
< 25 kg/m^2	53.2 (2266)
25-30 kg/m^2	33.0 (1405)
>30 kg/m^2	12.1 (516)
Missing	1.4 (74)
Smoking, % (N)	
Never	39.5 (1684)
Ever	43.2 (1842)
Missing	17.3 (735)
Physical activity, % (N)	
< 1 hour/week	3.8 (160)
≥ 1 hour/week	95.1 (4051)
Missing	1.2 (50)
Oral contraceptive use, % (N)	
Never	23.6 (1006)
Ever	75.3 (3209)
Missing	1.1 (46)
Hormone replacement therapy, % (N)	
Never	48.4 (2064)
Ever	36.6 (1561)
Missing	14.9 (636)
Tumor characteristics	
Tumor size, % (N)	
≤ 10	27.5 (1172)
11-20	44.8 (1907)
21-30	16.3 (694)
31-40	5.1 (219)
>40	4.5 (193)
Missing	1.8 (76)
Histological grade, % (N)	
Low	12.6 (537)
Moderate	33.3 (1418)
High	17.3 (739)
Missing	36.8 (1567)
No. of affected lymph nodes, % (N)	
0	64.2 (2734)
1-4	26.7 (1137)
>4	6.3 (269)
Missing	2.8 (121)
Treatment characteristics	
Surgery, % (N)	
Partial mastectomy	64.9 (2767)
Total mastectomy	34.7 (1477)
Missing	0.4 (17)
Radiotherapy, % (N)	
No	21.6 (920)
Yes	78.4 (3340)
Missing	0.0 (1)

All variables refer to the date of breast cancer diagnosis, except for body mass index, which was assessed at study entry in 2009. Missing on all variables less than 5%, except for smoking (17.3%) and histological grade (36.8%). Information on histological grade was only routinely collected in the Stockholm Breast Cancer Register from 2004 onward.

Supplementary Table 4. Chemotherapy and VTE risk in breast cancer patients - analyses by chemotherapy agent and stratified by endocrine therapy.

		N all/VTE cases	HR (95% CI)
All patients	Chemotherapy agent		
	No	2613/144	REF
	Yes, anthracyclines	786/64	2.08 (1.41-3.06)
	Yes, CMF	40/6	2.39 (1.01-5.68)
	Yes, taxanes	96/9	2.78 (1.28-6.04)
	Yes, type unspecified	721/52	1.84 (1.21-2.79)
Endocrine therapy	Chemotherapy		
No	No	171/6	REF
	Yes	521/39	2.48 (0.86-7.18)
Yes	No	2442/138	REF
	Yes	1127/93	2.07 (1.39-3.06)

Abbreviations: HR = hazard ratio; CI = confidence interval; CMF = cyclophosphamide, methotrexate and 5-fluorouracil; VTE = venous thromboembolism. All hazard ratios are multivariable adjusted (model 4).

Supplementary Table 5. Venous thromboembolism risk in breast cancer patients by chemotherapy and FVL carriership.

		HR (95% CI)			
	N all/ VTE cases	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Chemotherapy					
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)
FVL carrier					
No	3920/238	REF	REF	REF	REF
Yes	341/38	1.88 (1.33-2.64)	1.91 (1.35-2.70)	1.87 (1.32-2.65)	1.93 (1.36-2.74)
Chemotherapy/FVL carriership					
no chemo / no FVL carrier	2268/123	REF	REF	REF	REF
chemo / no FVL carrier	1414/115	1.85 (1.42-2.41)	1.82 (1.39-2.37)	1.86 (1.33-2.62)	1.96 (1.37-2.82)
no chemo / no FVL carrier	201/21	1.86 (1.17-2.96)	1.86 (1.16-2.97)	1.84 (1.15-2.95)	1.85 (1.15-2.96)
chemo / FVL carrier	102/17	3.79 (2.27-6.35)	3.92 (2.33-6.59)	3.83 (2.18-6.75)	4.10 (2.31-7.27)

Abbreviations: HR = hazard ratio; CI = confidence interval; FVL = factor V Leiden mutation carrier; 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)

Supplementary Table 6. Hazard ratios for venous thromboembolism (VTE) in breast cancer patients by chemotherapy and genetic susceptibility – sensitivity analyses (I-IV).

	Main		**Analysis I**		**Analysis II**		**Analysis III**		**Analysis IV**	
	N all/VTE	**HR (95% CI)**	**N all/VTE**	**HR (95% CI)**	**N all/VTE**	**HR (95% CI)**	**N all/VTE**	**HR (95% CI)**	**N all/VTE**	**HR (95% CI)**
Chemotherapy										
No	2613/144	REF	1117/39	REF	2553/122	REF	2613/132	REF	1298/65	REF
Yes	1648/132	1.98 (1.40-2.80)	821/66	2.70 (1.51-4.84)	1618/118	2.03 (1.40-2.94)	1648/119	2.25 (1.56-3.25)	932/78	2.27 (1.39-3.72)
PRS (percentiles)										
< 95%	4048/252	REF	1852/97	REF	3965/220	REF	4048/229	REF	2134/130	REF
≥ 95%	213/24	1.90 (1.24-2.91)	86/8	2.01 (0.95-4.23)	206/20	1.95 (1.23-3.10)	213/22	1.90 (1.21-2.97)	96/13	2.43 (1.35-4.37)
Chemotherapy/PRS (percentiles)										
no chemo / PRS < 95%	2474/130	REF	1060/36	REF	2419/110	REF	2474/120	REF	1236/59	REF
chemo / PRS < 95%	1574/122	1.98 (1.39-2.82)	792/61	2.59 (1.43-4.69)	1546/110	2.05 (1.40-2.99)	1574/109	2.23 (1.53-3.24)	898/71	2.23 (1.34-3.69)
no chemo / PRS ≥ 95%	139/14	1.87 (1.06-3.28)	57/3	1.66 (0.51-5.43)	134/12	2.15 (1.18-3.91)	139/12	1.73 (0.94-3.18)	62/6	2.29 (0.98-5.34)
chemo / PRS ≥ 95%	74/10	3.84 (1.91-7.71)	29/5	6.00 (2.09-17.25)	72/8	3.51 (1.63-7.59)	74/10	4.76 (2.34-9.66)	34/7	5.72 (2.35-13.91)

Abbreviations: HR = hazard ratio; CI = confidence interval; PRS = polygenic risk score. Sensitivity analyses: I = analysis requiring each patient with a VTE diagnosis to have a prescription of a vitamin K antagonist or heparin within 90 days or death within 30 days of the VTE event. This analysis was conducted in patients diagnosed after July 2005 with prescription data (N = 1938); II = analysis including patients without a VTE episode prior to diagnosis (N = 4171); III = analyses with additional censoring at recurrent events, defined as distant metastasis, locoregional recurrence and second primary cancer (N = 4261); IV = analysis including patients diagnosed from January 2005 onwards (N = 2230). All hazard ratios are multivariable adjusted (model 4).

Supplementary Table 7. Cumulative incidences of VTE by chemotherapy and genetic susceptibility – sensitivity analyses (I-IV).

			Cumulative incidence, %			
		N	6-months	1-year	2-year	5-year
Main	Chemotherapy					
	No	2613	0.9	1.4	2.2	4.0
	Yes	1648	4.1	5.2	5.6	6.7
	PRS (percentiles)					
	< 95%	4048	2.0	2.7	3.3	4.8
	≥ 95%	213	4.7	6.1	7.5	9.9
	Chemotherapy/PRS (percentiles)					
	no chemo / PRS < 95%	2474	0.7	1.3	2.0	3.7
	chemo / PRS < 95%	1574	3.9	5.0	5.3	6.4
	no chemo / PRS ≥ 95%	139	3.6	4.3	5.8	7.9
	chemo / PRS ≥ 95%	74	6.8	9.5	10.8	13.5
Analysis I	Chemotherapy					
	No	1117	0.3	0.8	1.3	3.1
	Yes	821	5.0	6.1	6.5	7.2
	PRS (percentiles)					
	< 95%	1852	2.2	2.9	3.3	4.6
	≥ 95%	86	4.7	7.0	8.1	9.3
	Chemotherapy/PRS (percentiles)					
	no chemo / PRS < 95%	1060	0.2	0.7	1.1	2.9
	chemo / PRS < 95%	792	4.8	5.8	6.2	6.8
	no chemo / PRS ≥ 95%	57	1.8	3.5	5.3	5.3
	chemo / PRS ≥ 95%	29	10.3	13.8	13.8	17.2
Analysis II	Chemotherapy					
	No	2553	0.6	1.1	1.8	3.4
	Yes	1618	3.8	4.8	5.2	6.1
	PRS (percentiles)					
	< 95%	3965	1.7	2.4	3.0	4.2
	≥ 95%	206	4.4	5.3	6.8	8.7
	Chemotherapy/PRS (percentiles)					
	no chemo / PRS < 95%	2419	0.5	1.0	1.7	3.2
	chemo / PRS < 95%	1546	3.6	4.7	5.0	5.9
	no chemo / PRS ≥ 95%	134	3.0	3.7	5.2	7.5
	chemo / PRS ≥ 95%	72	6.9	8.3	9.7	11.1
Analysis III	Chemotherapy					
	No	2613	0.8	1.4	2.2	3.9
	Yes	1648	4.1	5.2	5.5	6.6
	PRS (percentiles)					
	< 95%	4048	2.0	2.7	3.3	4.7
	≥ 95%	213	4.7	6.1	7.5	9.6
	Chemotherapy/PRS (percentiles)					
	no chemo / PRS < 95%	2474	0.7	1.3	2.0	3.7
	chemo / PRS < 95%	1574	3.9	5.0	5.3	6.2
	no chemo / PRS ≥ 95%	139	3.6	4.3	5.8	7.3
	chemo / PRS ≥ 95%	74	6.8	9.6	11.0	13.9
Analysis IV	Chemotherapy					
	No	1298	0.6	1.4	2.2	4.2
	Yes	932	4.9	6.3	6.6	7.4
	PRS (percentiles)					
	< 95%	2134	2.3	3.2	3.7	5.2
	≥ 95%	96	6.3	9.4	10.4	13.6
	Chemotherapy/PRS (percentiles)					
	no chemo / PRS < 95%	1236	0.5	1.3	1.9	4.0
	chemo / PRS < 95%	898	4.7	5.9	6.1	6.9
	no chemo / PRS ≥ 95%	62	3.2	6.5	9.7	9.7
	chemo / PRS ≥ 95%	34	11.8	17.7	17.7	20.6

Abbreviations: Cumulative incidences of VTE by chemotherapy and genetic susceptibility, at different time points following diagnosis. Abbreviations: PRS = polygenic risk score. Sensitivity analyses: I = analysis requiring each patient with a VTE diagnosis to have a prescription of a vitamin K antagonist or heparin within 90 days or death within 30 days of the VTE event. This analysis was conducted in patients diagnosed after July 2005 with prescription data (N = 1938); II = analysis including patients without a VTE episode prior to diagnosis (N = 4171); III = analyses with additional censoring at recurrent events, defined as distant metastasis, locoregional recurrence and second primary cancer (N = 4261); IV = analysis including patients diagnosed from January 2005 onwards (N = 2230). Cumulative incidences as obtained from Kaplan-Meier analysis with time since diagnosis as underlying time scale.