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

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Supplementary Table 1. International Classification of Diseases (ICD) codes used for defining venous thromboembolism.

	ICD-9	ICD-10
Venous thromboembolism	415B, 451B, 452, 453C-453D, 453W, 453X	I26, I80.1-I80.2, I81, I82.2-I82.9
Pulmonary embolism	415B	I26
Deep vein thrombosis	451B, 452, 453C-453D, 453W, 453X	I80.1-I80.2, I81, I82.2-I82.9

Abbreviations: ICD = International Coding of Disease classification. ICD codes for venous thromboembolism. Only primary diagnoses were considered valid.

Supplementary Table 2. Incidence rates for VTE in breast cancer patients and age-matched reference individuals from the general population.

	Breast cancer cohort			Matched population cohort		
	N all/events *	Person-years	Rate / 1000 yrs (95% CI)	N all/events	Person-years	Rate / 1000 yrs (95% CI)
Venous thromboembolism	8338/364	45915.52	7.9 (7.2-8.8)	39013/555	230713.15	2.4 (2.2-2.6)
Deep vein thrombosis	8338/235	46243.18	5.1 (4.5-5.8)	39013/358	231177.98	1.6 (1.4-1.7)
Pulmonary embolism	8338/141	46787.99	3.0 (2.6-3.6)	39013/227	231717.30	1.0 (0.9-1.1)

Abbreviations: HR = hazard ratio; CI = confidence interval. Follow-up started from the breast cancer diagnosis and corresponding index date in the age-matched reference individuals.* No. of incident VTE events is lower than in the Stockholm-Gotland breast cancer cohort with extended follow-up until December 2012.

Supplementary Table 3. Association of comorbidities, progesterone receptor status and chemotherapy with venous thromboembolism risk in breast cancer patients, overall and at specific time points after diagnosis.

	N total/VTE	HR (95% CI)						
		Overall	6 months	1 year	2 years	5 years	7 years	9 years
Comorbidities								
None	7385/360	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
1	514/38	1.28 (0.91-1.80)	0.92 (0.41-2.09)	0.74 (0.34-1.58)	0.89 (0.52-1.52)	1.59 (1.07-2.30)	2.11 (1.24-3.59)	2.58 (1.31-5.09)
≥ 2	439/28	1.16 (0.78-1.73)	0.78 (0.32-1.91)	1.02 (0.52-1.99)	1.20 (0.68-2.12)	1.36 (0.85-2.18)	1.45 (0.74-2.87)	1.52 (0.64-3.61)
Progesterone receptor status								
Positive	5176/236	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Negative	2419/143	1.33 (1.03-1.71)	1.38 (0.89-2.15)	1.19 (0.82-1.74)	1.14 (0.82-1.59)	1.54 (1.17-2.04)	1.85 (1.29-2.65)	2.09 (1.35-3.23)
Chemo/endocrine therapy								
None	355/11	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Endocrine only	4475/208	1.86 (0.94-3.72)	2.00 (0.60-6.68)	2.03 (0.58-7.15)	1.93 (0.67-5.59)	2.14 (0.92-4.95)	2.35 (0.68-8.10)	2.51 (0.52-12.04)
Chemo only	1119/66	2.42 (1.24-4.73)	11.87 (3.50-40.3)	6.94 (1.87-15.73)	1.69 (0.45-6.38)	0.92 (0.23-3.72)	0.61 (0.04-10.4)	0.45 (0.04-10.34)
Chemo plus endocrine	2230/131	2.74 (1.33-5.63)	9.39 (2.75-32.1)	3.11 (0.79-12.18)	1.16 (0.36-3.72)	1.93 (0.79-4.73)	2.06 (0.57-7.48)	2.11 (0.42-10.61)

Abbreviations: CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism. Time-dependent hazard ratios as estimated from flexible parametric survival models with time since diagnosis as underlying time scale, allowing the effect of each characteristic to vary over time. Hazard ratios are from multivariable adjusted models including time-dependent effects of all three variables.

Supplementary Table 4. Association of chemo/endocrine therapy with venous thromboembolism risk in breast cancer patients, overall and at specific time points after diagnosis.

	N total/VTE	HR (95% CI)						
		Overall	6 months	1 year	2 years	5 years	7 years	9 years
Chemo/endocrine therapy								
Other	355/11	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Tamoxifen only	3084/118	1.78 (0.88-3.62)	1.13 (0.35-3.67)	2.15 (0.70-6.62)	2.45 (0.92-6.53)	2.14 (1.00-4.59)	1.98 (0.80-4.95)	1.90 (0.65-5.55)
AI only	1289/84	2.16 (1.06-4.42)	2.96 (0.93-9.42)	2.66 (0.81-8.75)	2.29 (0.83-6.29)	1.97 (0.89-4.36)	1.82 (0.69-4.83)	1.73 (0.55-5.44)
Chemo only	1119/66	2.41 (1.23-4.71)	11.47 (3.78-35.8)	7.96 (2.47-25.7)	1.87 (0.54-6.53)	0.85 (0.21-3.35)	0.55 (0.04-6.86)	0.41 (0.01-13.0)
Chemo plus tamoxifen	1099/35	1.68 (0.77-3.66)	2.57 (0.70-9.46)	2.03 (0.53-7.71)	1.66 (0.53-5.21)	1.53 (0.64-3.63)	1.45 (0.50-4.23)	1.40 (0.40-4.92)
Chemo plus AI	1074/93	3.87 (1.84-8.12)	14.89 (4.81-46.1)	5.25 (1.50-18.40)	1.26 (0.34-4.70)	2.17 (0.90-5.23)	2.07 (0.70-6.11)	1.96 (0.56-6.87)

Association of chemo/endocrine therapy with venous thromboembolism risk, subdivided by type of intended endocrine therapy at diagnosis. Time-dependent hazard ratios as estimated from flexible parametric survival models with time since diagnosis as underlying time scale, allowing the effect of each exposure category to vary over time. All analyses are multivariable adjusted including all patient, tumor and treatment-related factors with inclusion of all time-dependent effects.

Supplementary Table 5. Incidence rates and hazard ratios for venous thromboembolism in breast cancer patients compared to age-matched reference individuals from the general population– sensitivity analysis requiring each patient with a VTE diagnosis to also fill a prescription of vitamin K antagonists or heparins within 90 days, or to have died within 30 days of the event.

	Breast cancer patients			Matched population cohort			HR (95% CI) †
	N all/events *	Person-years	Rate / 1000 yrs (95% CI)	N all/events	Person-years	Rate / 1000 yrs (95% CI)	
Main analysis prescription cohort (2005-2008)							
Venous thromboembolism	3619/133	13016.47	10.2 (8.6-12.1)	16543/163	61988.33	2.6 (2.3-3.1)	3.86 (3.07-4.85)
Deep vein thrombosis	3619/89	13100.19	6.8 (5.5-8.4)	16543/100	62110.44	1.6 (1.3-2.0)	4.19 (3.15-5.57)
Pulmonary embolism	3619/48	13249.30	3.6 (2.7-4.8)	16543/71	62143.61	1.1 (0.9-1.4)	3.16 (2.19-4.56)
Sensitivity analysis prescription cohort (2005-2008)							
Venous thromboembolism	3619/119	13052.08	9.1 (7.6-10.9)	16543/143	62017.40	2.3 (2.0-2.7)	3.93 (3.08-5.08)
Deep vein thrombosis	3619/78	13127.14	5.9 (4.8-7.4)	16543/86	62133.99	1.4 (1.1-1.7)	4.26 (3.14-5.79)
Pulmonary embolism	3619/45	13257.96	3.4 (2.5-4.6)	16543/64	62150.58	1.0 (0.9-1.3)	3.29 (2.24-4.81)

Abbreviations: HR = hazard ratio; CI = confidence interval. Incidence rates and hazard ratios of VTE in breast cancer patients diagnosed after July 2005 (prescription cohort) compared to their age-matched reference individuals from the general population. Main analyses refer to the analysis based on diagnostic codes only; Sensitivity analysis refers to analysis requiring with verification of VTE diagnoses. * No. of incident VTE events is lower than in the Stockholm-Gotland breast cancer cohort with extended follow-up until December 2012. † Hazard ratios are somewhat increased as compared to those observed in the total cohort (2001-2008, N = 8338), as a result of the time-dependent VTE risk pattern and shortened follow-up in the prescription cohort (2005-2008).

Supplementary Table 6. Risk of venous thromboembolism in breast cancer patients compared to age-matched reference individuals from the general population, overall and at specific time points after the index date – sensitivity analysis with additional censoring at recurrent events.

		HR (95% CI)						
		Overall	At 6 months	At 1 year	At 2 years	At 5 years	At 7 years	At 9 years
	N total/VTE *							
Matched population cohort	39013/533	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8338/315	3.04 (2.65-3.50)	8.83 (6.69-11.7)	4.20 (3.28-5.38)	1.75 (1.27-2.40)	1.78 (1.41-2.39)	1.76 (1.28-2.42)	1.65 (1.12-2.42)
	N total/DVT *							
Matched population cohort	39013/343	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8338/215	3.19 (2.69-3.79)	10.53 (7.43-14.9)	3.24 (2.24-4.69)	1.53 (1.04-2.25)	1.89 (1.40-2.55)	2.00 (1.34-2.99)	1.95 (1.22-3.12)
	N total/PE *							
Matched population cohort	39013/220	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (.100)
Breast cancer cohort	8338/112	2.62 (2.08-3.29)	6.90 (4.42-10.8)	4.28 (2.96-6.19)	2.07 (1.27-3.37)	1.67 (1.20-2.33)	1.43 (0.87-2.37)	1.26 (0.66-2.39)

Abbreviations: HR = hazard ratio; CI = confidence interval; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism. Hazard ratios were estimated using flexible parametric survival models. Follow-up in all patients and age-matched reference individuals started at the index date (= date of diagnosis for breast cancer patients), and follow-up was complete until December 2010. Person-time was censored at disease recurrence (defined as locoregional recurrence or distant metastasis) and diagnosis of a new primary breast cancer after the index date. * No. of incident VTE events is lower than in the Stockholm-Gotland breast cancer cohort with extended follow-up until December 2012.

Supplementary Table 7. Risk of venous thromboembolism in breast cancer patients compared to age-matched reference individuals from the general population, overall and at specific time points after the index date – sensitivity analysis in individuals without a VTE diagnosis prior to the index date.

		HR (95% CI)						
		Overall	At 6 months	At 1 year	At 2 years	At 5 years	At 7 years	At 9 years
	N total/VTE *							
Matched population cohort	38547/484	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8227/321	3.33 (2.89-3.81)	9.75 (7.19-13.2)	4.63 (3.38-6.34)	2.12 (1.56-2.89)	2.15 (1.75-2.63)	2.17 (1.60-2.93)	2.07 (1.41-3.04)
	N total/DVT *							
Matched population cohort	38547/311	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8227/202	3.23 (2.70-3.85)	10.53 (7.23-15.3)	3.72 (2.42-5.73)	1.86 (1.27-2.71)	1.92 (1.44-2.57)	2.13 (1.43-3.18)	2.11 (1.31-3.40)
	N total/PE *							
Matched population cohort	38547/196	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Breast cancer cohort	8227/127	3.24 (2.59-4.05)	9.67 (5.70-16.4)	6.02 (3.79-9.57)	2.80 (1.86-4.20)	2.24 (1.65-3.04)	2.28 (1.48-3.51)	2.19 (1.23-3.92)

Abbreviations: HR = hazard ratio; CI = confidence interval; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism. Hazard ratios were estimated using flexible parametric survival models. Follow-up in all patients and age-matched reference individuals started at the index date (= date of diagnosis for breast cancer patients), and follow-up was complete until December 2010. Sensitivity analyses excluding individuals with a VTE diagnosis prior to the index date. * No. of incident VTE events is lower than in the Stockholm-Gotland breast cancer cohort with extended follow-up until December 2012.

Supplementary Table 8. Association of patient, tumor and treatment characteristics with risk of venous thromboembolism risk in breast cancer patients without a diagnosis of VTE prior to breast cancer (N = 8227).

	N total/VTE	HR (95% CI)		
		Model 1	Model 2	Model 3
Patient characteristics				
Age at diagnosis (years)				
< 50	1837/58	REF (1.00)	REF (1.00)	REF (1.00)
50-59	2613/110	1.27 (0.93-1.75)	1.28 (0.93-1.77)	1.41 (1.02-1.94)
60-69	2833/154	1.75 (1.29-2.36)	1.73 (1.28-2.35)	2.02 (1.48-2.78)
> 69	944/60	2.18 (1.52-3.13)	2.01 (1.40-2.91)	2.46 (1.66-3.65)
BMI (kg/m ²)				
<25	2518/85	REF (1.00)	REF (1.00)	REF (1.00)
25-30	1539/70	1.35 (0.98-1.85)	1.35 (0.98-1.85)	1.32 (0.96-1.82)
> 30	571/30	1.54 (1.02-2.34)	1.51 (0.99-2.29)	1.48 (0.98-2.36)
Comorbidities *				
None	7297/324	REF (1.00)	REF (1.00)	REF (1.00)
1	502/33	1.39 (0.97-1.99)	1.30 (0.91-1.88)	1.32 (0.92-1.91)
≥ 2	428/25	1.31 (0.87-1.98)	1.24 (0.82-1.88)	1.27 (0.84-1.92)
Tumor characteristics				
Tumor size (mm)				
≤ 10	2059/82	REF (1.00)	REF (1.00)	REF (1.00)
11-20	3508/159	1.18 (0.91-1.54)	1.17 (0.88-1.56)	1.08 (0.81-1.44)
21-40	1898/92	1.36 (1.01-1.83)	1.14 (0.82-1.58)	1.03 (0.73-1.44)
>40	505/40	2.37 (1.62-3.46)	1.72 (1.14-2.62)	1.52 (0.98-2.36)
Tumor grade (Elston)				
Low	952/32	REF (1.00)	REF (1.00)	REF (1.00)
Moderate	2512/102	1.22 (0.82-1.81)	1.05 (0.70-1.57)	1.04 (0.69-1.56)
High	1521/68	1.51 (0.99-2.29)	1.12 (0.71-1.75)	1.00 (0.64-1.59)
Estrogen receptor status				
Positive	6262/279	REF (1.00)	REF (1.00)	REF (1.00)
Negative	1364/70	1.26 (0.97-1.64)	0.98 (0.71-1.35)	1.00 (0.61-1.63)
Progesterone receptor status *				
Positive	5105/211	REF (1.00)	REF (1.00)	REF (1.00)
Negative	2389/129	1.39 (1.12-1.74)	1.32 (1.01-1.71)	1.32 (1.01-1.73)
No. of affected lymph nodes				
0	4964/197	REF (1.00)	REF (1.00)	REF (1.00)
1-4	2214/103	1.26 (0.99-1.60)	1.21 (0.95-1.55)	1.06 (0.80-1.39)
> 4	703/63	2.75 (2.07-3.66)	2.38 (1.75-3.25)	1.95 (1.35-2.84)
Treatment characteristics				
Surgery				
Total mastectomy	3154/160	REF (1.00)	REF (1.00)	REF (1.00)
Breast-conserving	4955/217	0.80 (0.65-0.99)	0.79 (0.61-1.03)	1.09 (0.81-1.48)
Radiotherapy				
No	1846/79	REF (1.00)	REF (1.00)	REF (1.00)
Yes	6244/297	1.17 (0.91-1.50)	1.33 (0.98-1.80)	1.00 (0.72-1.39)
Chemo/endocrine therapy *				
None	349/8	REF (1.00)	REF (1.00)	REF (1.00)
Endocrine only	4405/184	1.97 (0.97-4.00)	1.96 (0.93-3.97)	2.32 (1.07-5.08)
Chemo only	1109/62	3.64 (1.74-7.64)	3.41 (1.62-7.18)	3.17 (1.47-6.83)
Chemo plus endocrine	2206/119	3.38 (1.64-6.95)	3.10 (1.50-6.42)	3.20 (1.42-7.19)

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