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

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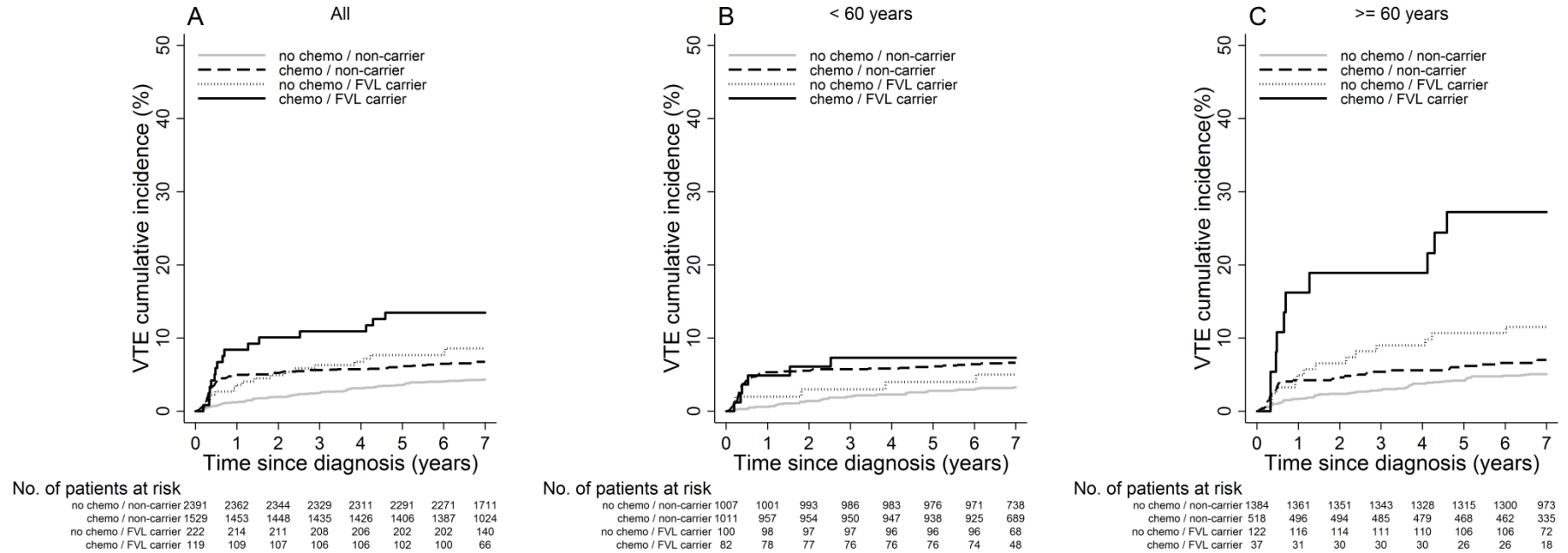
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Supplementary Figure 1. Cumulative incidence of VTE by chemotherapy and FVL carriership, overall and stratified by age at diagnosis.

Supplementary Figure 1



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).

Supplementary material to: Judith S. Brand, Elham Hedayati, Keith Humphreys, Jonas F. Ludvigsson, Anna L.V. Johansson, Jonas Bergh, Per Hall, Kamila Czene; Chemotherapy, Genetic Susceptibility, and Risk of Venous Thromboembolism in Breast Cancer Patients. Clin Cancer Res 1 November 2016; 22 (21): 5249–5255. <https://doi.org/10.1158/1078-0432.CCR-16-1110>

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.

| | N all/ VTE cases | HR (95% CI) | | | |
|-------------------------------------|------------------|------------------|------------------|------------------|------------------|
| | | 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 / 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).

| | | N | Cumulative incidence, % | | | |
|---------------------|--------------------------------|------|-------------------------|--------|--------|--------|
| | | | 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.