**Supplementary Figures and Tables**

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

Judith S. Brand, Elham Hedayati, Keith Humphreys, Jonas F. Ludvigsson, Anna L.V. Johansson, Jonas Bergh, Per Hall, Kamila Czene.

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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).

**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/m2 | 53.2 (2266) |
|  25-30 kg/m2 | 33.0 (1405) |
|  >30 kg/m2 | 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.