**Supplementary Materials and Methods. Estimation of 10-year Absolute Breast Cancer Risk**

From the NHS case-control dataset we obtain the RR estimate given by

RR = exp(S) = exp(β1 QS + β2 MD + β3 PRS) = exp($\sum\_{q=1}^{3}β\_{q}x\_{q}$).

We then divide the NHS case-control dataset into 6 age strata defined by

 age = (45-49/50-54/55-59/60-64/65-69/70-74). We define a woman as being at baseline risk if

$\overline{x}$ = ($x\_{1},x\_{2},x\_{3}$) = $\overline{0}$.

Let

N*l* = number of women in the *l*th age stratum in 1990, *l =* 1,…,L*,*

Y*l* = observed number of cases in the *l*th age stratum, *l =* 1,…,L*,*

O*il* = 1 if the *i*th woman in the *l*th age stratum becomes a case from 1990-2000,

 = 0 otherwise,

RR*il* = relative risk for the ith woman in the *l*th age stratum, *i* = 1,…, N*l*, *l* = 1,…,6,

$F\_{l}$ = ( $\sum\_{i=1}^{N\_{l}}1/RR\_{il}$)/$Y\_{l}$, *l* = 1,…,6,

h\*(*l*) = 100,000 \* age-specific incidence rate from SEER 1995

 = (253.3, 336.8, 417.0, 494.2, 538.8, 579.3),

$h\_{10}^{\*}(l)$ = estimated 10-year age-specific incidence rate from SEER

 = 1 – exp[-10$h^{\*}$(*l*)], *l* = 1,…,6.

Following Gail (37), we estimate the 10-year baseline risk for a woman in the *l*th age stratum by

$h\_{10,0}\left(l\right)=h\_{10}^{\*}$ (*l*) $F\_{l}$.

The 10-year absolute risk for the *i*th woman in the *lth* age stratum is then given by

$\hat{P}\_{10,il}=h\_{10,0}\left(l\right)RR\_{il},i=1,…,N\_{l},l=1,…,6.$

In the NHS data, Y*l* = (80, 113, 133, 137, 0) and N*l* = (164, 248, 288, 306, 159, 1). Due to the small number in age group 70-74 (age group 6) the above calculations were restricted to the age range 45- 69 (age groups 1-5). The resulting value of  are given by

$h\_{10,0}\left(l\right)=$ (346.1, 432.4, 531.4, 665.6, 901.2) per 105 person-years.

The $P\_{10,il}$ were then categorized as follows: (< 2%, 2.0-2.9%, 3.0-4.9%, 5.0-7.9%, $\geq $ 8%)

and cross-classified by case-control status as shown in Table 5 and Figures 1A-1B.

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| **Supplemental Table S1. Breast cancer risk factors assessed in the Nurses’ Health Study and their inclusion in Rosner-Colditz and reduced breast cancer risk prediction models** |
| Category  | Risk factor | Assessed in NHS | Rosner-Colditz | Simplified Rosner-Colditz  |
|  | Age in years | Yes | No | Yes |
|  | Age at menarche | Yes | No | No |
| Parity | Age at first live birth | Yes | No | Yes |
|  | Parous (yes/no) | Yes | No | No |
|  | Gynecological age at first birth | Yes | Yes | No |
|  | Birth index | Yes | Yes | No |
| Menopause | Age at menopause | Yes | No | No |
|  | Duration of menopause | Yes | No  | Yes |
|  | Duration of premenopause | Yes | Yes | No |
|  | Duration of natural menopause | Yes | Yes | No |
|  | Duration of menopause if BOO | Yes | Yes | No |
| Hormone therapy | Current HT use | Yes | Yes | Yes |
|  | Past HT use | Yes | Yes | no |
|  | Current combined HT (E&P) | Yes | No | Yes |
|  | Current estrogen alone | Yes |  | Yes |
|  | Current progesterone alone  | Yes |  | Yes |
|  | Years of HT use | Yes | No | No |
|  | Time since last HT use | Yes | No | No |
|  | Duration of oral E+P use | Yes | Yes | No |
|  | Duration of oral E alone use | Yes | Yes | No |
|  | Duration of other postmenopausal HT | Yes | Yes | No |
| Anthropometry  | Height | Yes | No | Yes  |
|  | Weight | Yes | No | Yes as current BMI |
|  | Premenopausal BMI x yrs premenopausal | Yes | Yes | No |
|  | Postmenopausal BMI x yrs menopausal | Yes | Yes | No |
|  | Height x yrs premenopausal | Yes | Yes | No |
|  | Height x yrs menopausal | Yes | Yes | No |
| Alcohol | Current total alcohol ounces | Yes | No | Yes |
|  | Total alcohol ounces premenopause | Yes | Yes | No |
|  | Alcohol ounces with HT postmenopause | Yes | Yes | No |
|  | Alcohol ounces without HT postmenopause | Yes | Yes | No |
| Benign breast disease | Benign breast disease (BBD, yes/no) | Yes | Yes | Yes |
|  | BBD x age at menarche | Yes | Yes | No |
|  | BBD x duration of premenopause | Yes | Yes | No |
|  | BBD x duration of menopause | Yes | Yes | No |
|  | Number of breast biopsies (0, 1, or >1) | Only 1 vs ≥1 | No | No |
| Family history  | Breast cancer in 1st degree relative | Yes | Yes | Yes |

|  |
| --- |
| **Supplementary Table S2: Distribution of Risk Factors in 1990 by case/control status in women with mammographic density\*\*\*** |
| **Variable categories**  | **Cases** | **Controls** |
|  | N(%) | N(%) |
| **N** | 533 | 633 |
|  |  |  |
| **Age, menopausal status, N(%)** |  |  |
| age 45-49, premenopausal | 44(8.3%) | 53(8.4%) |
| age 50-59, premenopausal | 56(10.5%) | 56(8.9%) |
| age 45-49, postmenopausal | 7(1.3%) | 7(1.1%) |
| age 50-54, postmenopausal | 52(9.8%) | 69(10.9%) |
| age 55-59, postmenopausal | 114(21.4%) | 130(20.5%) |
| age 60-64, postmenopausal | 123(23.1%) | 168(26.5%) |
| age 65-74, postmenopausal | 129(24.2%) | 140(22.1%) |
|  |  |  |
| **Menopausal status, N(%)** |  |  |
|  Pre | 100(18.8%) | 109(17.2%) |
|  Post | 433(81.2%) | 524(82.8%) |
|  |  |  |
| **Duration of post-menopause, mean(sd)\*\*\*\*** | 11.6(6.6) | 11.4(6.6) |
|  |  |  |
| **Pregnancy History, N(%)** |  |  |
| Nulliparous | 37(6.9%) | 35(5.5%) |
| age 1st birth 20-24  | 240(45.0%) | 305(48.2%) |
| age 1st birth 25-29  | 213(40.0%) | 235(37.1%) |
| age 1st birth 30+ | 43(8.1%) | 58(9.2%) |
|  |  |  |
| **BBD(Biopsy confirmed), N(%)** | 152(28.5%) | 119(18.8%) |
|  |  |  |
| **Family history BRCN, N(%)** | 76(14.3%) | 83(13.1%) |
|  |  |  |
| **Current PMH use, N(%)\*** |  |  |
|  No | 245(46.0%) | 331(52.3%) |
|  Estrogen | 130(24.4%) | 156(24.6%) |
|  E&P | 112(21.0%) | 99(15.6%) |
|  Progesterone alone | 9(1.7%) | 8(1.3%) |
|  Other\*\* | 37(6.9%) | 39(6.1%) |
|  |  |  |
| **Current BMI, pre-men, N (%)** |  |  |
|  <25 | 59(59.0%) | 67(61.5%) |
|  25-29.9 | 28(28.0%) | 31(28.4%) |
|  >=30 | 13(13.0%) | 11(10.1%) |
|  mean(sd) | 25.0(4.6) | 24.7(3.6) |
|  |  |  |
| **Current BMI, post-men, N(%)** |  |  |
|  <25 | 202(46.7%) | 272(51.9%) |
|  25-29.9 | 153(35.3%) | 161(30.7%) |
|  >=30 | 78(18.0%) | 91(17.4%) |
|  mean(sd) | 26.2(4.8) | 25.9(4.5) |
|  |  |  |
| **Height, mean(sd)** | 64.5(2.3) | 64.4(2.4) |
|  |  |  |
| **Current Alcohol, N(%)** |  |  |
|  None | 188(35.3%) | 207(32.7%) |
|  <11 gm/day | 247(46.3%) | 310(49.0%) |
|  11-21.9 gm/day | 62(11.6%) | 78(12.3%) |
|  >22 gm/day | 36(6.8%) | 38(6.0%) |
|  |  |  |
| \* Hormone therapy status unknown or missing use were deleted  |  |  |
|  \*\*Vaginal estrogen or vaginal progesterone or Other Brands, mixed use or Current user no brand given |  |
| \*\*\*cases from 1990 to 2000 |  |  |
| \*\*\*\*among post-menopausal women |  |  |
|  |  |  |
|  |  |

**Supplementary Table S3**

**AUCs for 10-year risk among women age>= 45 in 1990 from the Nurses' Health Study, and**

**from the Mayo Mammography Health Study validation data, using**

**BIRADs for mammographic breast density classification**

|  |
| --- |
|  |
|  | **AUC (NHS)** | **AUC (MMHS)** |
| Age alone | 0.523 | 0.595 |
| Age + BIRADs | 0.624 | 0.614 |
| Age + BIRADs + questionnaire score | 0.639 | 0.633 |
| Age + BIRADs + questionnaire score + polygenic risk score | 0.659 | 0.668 |
|  |  |  |
|  |  |  |

**Supplementary Table S4**

**Net reclassification Index for 10-year risk among women age>= 45 in 1990 for cases and controls** **from the Mayo Mammography Health Study validation data**

1. Cases (n=438)

|  |  |
| --- | --- |
|  **10-year expected incidence of breast cancer,**Age, MD, QS | **10-year expected incidence of breast cancer** Age, MD, QS and PRS |
|  | <0.02 (below average) | 0.02-0.029 (average) | 0.03-0.049 (above average) | 0.05-0.079 (moderately increased) | 0.08+ (high) |
| <0.02 (below average)  | 13 | 6 | 0 | 0 | 0 |
| 0.02-0.029 (average)  | 13 | 25 | 19 | 0 | 0 |
| 0.03-0.049 (above average)  | 2 | 30 | 78 | 50 | 2 |
| 0.05-0.079 (moderately increased) | 0 | 0 | 37 | 88 | 42 |
| 0.08+  (high) | 0 | 0 | 0 | 10 | 23 |

NRI=6%

1. Controls (n=898)

|  |  |
| --- | --- |
|  **10-year expected incidence of breast cancer,****Age, MD, QS** | **10-year expected incidence of breast cancer** **Age, MD, QS and PRS** |
|  | <0.02 (below average) | 0.02-0.029 (average) | 0.03-0.049 (above average) | 0.05-0.079 (moderately increased) | 0.08+ (high) |
| <0.02 (below average)  | 84 | 16 | 3 | 0 | 0 |
| 0.02-0.029 (average)  | 69 | 83 | 32 | 1 | 0 |
| 0.03-0.049 (above average)  | 19 | 113 | 183 | 65 | 2 |
| 0.05-0.079 (moderately increased) | 0 | 8 | 72 | 77 | 35 |
| 0.08+ (high) | 0 | 0 | 0 | 16 | 20 |

NRI=16%