CEBP MS EPI-18-1039

Comparison of questionnaire-based breast cancer prediction models in the Nurses’ Health Study

Supplemental Appendix

Supplemental table 1. Breast cancer risk factors assessed in the Nurses’ Health Study and their inclusion in breast cancer risk prediction models

|  |  |  |
| --- | --- | --- |
|  |  | Included in risk prediction model |
| Risk factor | Assessed in NHS | Gail (BCRAT) | Tyrer-Cuzick (IBIS) | Rosner-Colditz |
| Age at menarche | Yes | Yes | Yes | No |
| Age at first live birth | Yes | Yes | Yes | No |
| Age in years | Yes | Yes | Yes | No |
| Age at menopause | Yes | No | Yes | No |
| Parous (yes/no) | Yes | No | Yes | No |
| Duration of premenopause | Yes | No | No | Yes |
| Duration of natural menopause | Yes | No | No | Yes |
| Duration of menopause if BOO | Yes | No | No | Yes |
| Gynecological age at first birth | Yes | No | No | Yes |
| Birth index | Yes | No | No | Yes |
| Current or former hormone therapy | Yes | No | Yes | No |
| Combined HT vs estrogens alone | Yes | No | Yes | No |
| Years of HT use | Yes | No | Yes | No |
| Anticipated future years of HT use | No | No | Yes | No |
| Time since last HT use | Yes | No | Yes | No |
| Duration of oral E+P use | Yes | No | No | Yes |
| Duration of oral E alone use | Yes | No | No | Yes |
| Duration of other postmenopausal HT | Yes | No | No | Yes |
| Current HT use | Yes | No | No | Yes |
| Past HT use | Yes | No | No | Yes |
| Height | Yes | No | Yes | No |
| Weight | Yes | No | Yes | No |
| Premenopausal BMI x yrs premenopausal | Yes | No | No | Yes |
| Postmenopausal BMI x yrs menopausal | Yes | No | No | Yes |
| Height x yrs premenopausal | Yes | No | No | Yes |
| Height x yrs menopausal | Yes | No | No | Yes |
| Total alcohol ounces premenopause | Yes | No | No | Yes |
| Alcohol ounces with HT postmenopause | Yes | No | No | Yes |
| Alcohol ounces without HT postmenopause | Yes | No | No | Yes |
| Benign breast disease (BBD, yes/no) | Yes | No | No | Yes |
| BBD x age at menarche | Yes | No | No | Yes |
| BBD x duration of premenopause | Yes | No | No | Yes |
| BBD x duration of menopause | Yes | No | No | Yes |
| Atypical hyperplasia (yes/no) | No | Yes | Yes | No |
| Hyperplasia (yes/no) | No | No | Yes | No |
| Number of breast biopsies (0, 1, or >1) | Only 1 vs ≥1 | Yes | No | No |
| History of lobular carcinoma in situ | No | No | Yes | No |
| Ashkenazi heritage | No | No | Yes | No |
| History of ovarian cancer | Yes | No | Yes | No |
| BRCA1/2 mutation | No | No | Yes | No |
| BRCA1/2 mutation in father | No | No | Yes | No |
| Breast cancer in 1st degree relative | Yes | Yes | Yes | Yes |
| Breast cancer in 2nd degree relative | No\* | No | Yes | No |
| Breast cancer in 1st cousin | No | No | Yes | No |
| Age at diagnosis in relative | Yes† | No | Yes | No |
| Bilateral breast cancer in relative | No | No | Yes | No |
| BRCA1/2 in 1st, 2nd, or 3rd degree relative | No | No | Yes | No |
| Ovarian cancer in relative | Yes† | No | Yes | No |
| Age at diagnosis of ovarian cancer in relative | No | No | Yes | No |
| Number of biopsies x age 50 plus (yes, no) | No | Yes | No | No |
| Age at first birth x 1st degree relatives with breast cancer | Yes | Yes | No | No |
| Male breast cancer in 1st, 2nd, or 3rd degree relative | No‡ | No | Yes | No |

\*Information was available for grandmothers

†Available for 1st degree relatives

‡Available for father only

Supplemental table 2. Characteristics of women at the beginning of 2-year intervals from 1990-2006

|  |  |  |  |
| --- | --- | --- | --- |
|  | All intervals | With family history | Developed breast cancer within 2 years |
| N of intervals | 768,948 | 86,892 | 4,384 |
| Age at questionnaire | 57 (49, 65) | 61 (54, 68) | 60 (54, 67) |
| Caucasian race, % | 93.8 | 93.8 | 94.4 |
| Age at menarche | 13 (12, 13) | 13 (12, 13) | 12.5 (12, 13) |
| Post-menopausal, % | 72.4 | 82.3 | 82.2 |
| Natural menopause, %\* | 77.4 | 77.6 | 81.3 |
| Bilateral oophorectomy, %\* | 22.6 | 22.4 | 18.7 |
| Years since menopause† | 8 (0, 16) | 11 (3,19) | 10 (3, 18) |
| Parity  | 3 (2, 4) | 3 (2, 4) | 3 (2, 4) |
| Parous, % | 94.2 | 94.0 | 92.4 |
| Age at first birth‡ | 24 (23, 27) | 25 (23, 27) | 25 (23, 27) |
| Current use of hormone therapy, % | 24.2 | 24.4 | 35.4 |
| Past use of hormone therapy, % | 21.5 | 27.0 | 19.2 |
| Benign breast disease, % | 39.3 | 49.3 | 50.9 |
| Family history of breast cancer, % | 11.3 | 100.0 | 17.4 |
| Incident breast cancer during interval, % | 0.57 | 0.88 | 100.0 |

\*Among post-menopausal women

†Scored 0 for pre-menopausal women

‡Among parous women

Supplemental Table 3. Calibration of predictions from the Gail and Tyrer-Cuzick models in the Nurses’ Health Study: 616 incident breast cancer cases in 193,390 2-year intervals among women under age 50 at the beginning of the interval

|  |  |  |  |
| --- | --- | --- | --- |
| Gail model | Gail model calibration | Tyrer-Cuzick model | Tyrer-Cuzick model calibration |
| Risk decile cutpoints | Intervals, expected and observed cases | Risk decile cutpoints | Intervals, expected and observed cases |
| Predicted risk (%)\* | N | E/O | Ratio, (95% CI) | Predicted risk (%)\* | N | E/O (ratio) | Ratio, (95% CI) |
| .0249-.2485 | 77,672 | 140.6/181 | 0.78, (0.67, 0.90)‡ | .0258-.2644 | 75,071 | 138.5/170 | 0.81, (0.70, 0.95)‡ |
| .2486-.3474 | 60,575 | 182.0/199 | 0.91, (0.80, 1.05) | .2644-.3604 | 55,225 | 172.4/166 | 1.04, (0.89, 1.21) |
| .3480-.4020 | 28,622 | 107.8/93 | 1.16, (0.95, 1.42) | .3604-.4262 | 29,223 | 114.2/113 | 1.01, (0.84, 1.22) |
| .4023-.4755 | 9,900 | 43.8/37 | 1.18, (0.86, 1.63) | .4262-.4837 | 14,218 | 64.2/48 | 1.34, (1.01, 1.78)† |
| .4757-.5313 | 4,189 | 20.9/25 | 0.84, (0.57, 1.24) | .4837-.5428 | 7,009 | 35.8/36 | 0.99, (0.72, 1.38) |
| .5314-.6097 | 3,437 | 19.4/28 | 0.69, (0.48, 1.00) | .5428-.6089 | 3,789 | 21.7/20 | 1.08, (0.70, 1.68) |
| .6098-.6902 | 4,910 | 31.5/31 | 1.01, (0.71, 1.44) | .6089-.6909 | 2,489 | 16.1/22  | 0.73, (0.48, 1.11) |
| .6904-.8001 | 2,689 | 19.4/13 | 1.49, (0.86, 2.56) | .6909-.8101 | 2,492 | 18.6/14 | 1.33, (0.79, 2.25) |
| .8002-.9941 | 345 | 3.1/3 | 1.03, (0.33, 3.22) | .8101-1.042 | 2,889 | 26.2/19 | 1.38, (0.88, 2.16) |
| .9948-4.289 | 1,051 | 12.1/6 | 2.01, (0.90, 4.47) | 1.042-5.141 | 985 | 11.9/8 | 1.49, (0.74, 2.98) |
| Overall | 193,390 | 580.5/616 | 0.94, (0.87, 1.02) |  | 193,390  | 619.6/616 | 1.01, (0.93, 1.09) |
| Average (SD), min-max predicted risk (%) |  | 0.30 (0.15), 0.0249-2.518 |  | 0.32 (.16), .0258-3.492 |
|  | Hosmer-Lemeshow Chi square =26.03, d.f.=8, P=0.001  |  | Hosmer-Lemeshow Chi square=18.25, d.f.=8, P=0.019 |

E/O denotes expected number of breast cancer cases/observed number of cases

\*Predicted 2-year risk

†P<0.05 for test of the null hypothesis that E/O=1; ‡P<0.01 for test of the null hypothesis that E/O=1

Supplemental Table 4. Calibration of predictions from the Gail and Tyrer-Cuzick models in the Nurses’ Health Study: 1,441 incident breast cancer cases in 251,403 2-year intervals among women age 50-59 at the beginning of the interval

|  |  |  |  |
| --- | --- | --- | --- |
| Gail model | Gail model calibration | Tyrer-Cuzick model | Tyrer-Cuzick model calibration |
| Risk decile cutpoints | Intervals, expected and observed cases | Risk decile cutpoints | Intervals, expected and observed cases |
| Predicted risk (%)\* | N | E/O | Ratio, (95% CI) | Predicted risk (%)\* | N | E/O (ratio) | Ratio, (95% CI) |
| .0249-.2485 | 598 | 1.3/2 | 0.67, (0.17, 2.68) | .0258-.2644 | 1,441 | 3.4/3 | 1.14, (0.37, 3.55) |
| .2486-.3474 | 9,697 | 30.2/32 | 0.94, (0.67, 1.34) | .2644-.3604 | 17,112 | 55.9/54 | 1.04, (0.79, 1.35) |
| .3480-.4020 | 51,709 | 191.0/198 | 0.96, (0.84, 1.11) | .3604-.4262 | 35,005 | 138.7/130 | 1.07, (0.90, 1.27) |
| .4023-.4755 | 64,488 | 284.0/354 | 0.80, (0.72, 0.89)‡ | .4262-.4837 | 40,525 | 184.5/167 | 1.10, (0.95, 1.29) |
| .4757-.5313 | 46,077 | 234.0/256 | 0.91, (0.81, 1.03) | .4837-.5428 | 38,282 | 196.1/212 | 0.93, (0.81, 1.06) |
| .5314-.6097 | 33,038 | 189.2/200 | 0.95, (0.82, 1.09) | .5428-.6089 | 33,407 | 191.8/190 | 1.01, (0.88, 1.16) |
| .6098-.6902 | 13,710 | 90.4/109 | 0.83, (0.69, 1.00) | .6089-.6909 | 28,042 | 181.4/158  | 1.15, (0.98, 1.34) |
| .6904-.8001 | 10,094 | 75.2/78 | 0.96, (0.77,1.20) | .6909-.8101 | 22,444 | 166.8/177 | 0.94, (0.81,1.09) |
| .8002-.9941 | 13,429 | 120.1/123 | 0.98, (0.82, 1.17) | .8101-1.042 | 17,986 | 163.2/177 | 0.92, (0.80, 1.07) |
| .9948-4.289 | 8,563 | 102.5/89 | 1.15, (0.94, 1.42) | 1.042-5.141 | 17,159 | 233.2/173 | 1.35, (1.16, 1.56)‡ |
| Overall | 251,403 | 1318/1441 | 0.91, (0.87, 0.96)‡ |  | 251,403  | 1515.1/1,441 | 1.05, (1.00, 1.11) |
| Average (SD), min-max predicted risk (%) |  | 0.52 (0.19), 0.1601-3.261 |  | 0.60 (.27), 0.1524-4.473 |
|  | Hosmer-Lemeshow Chi square =26.41, d.f.=8, P<0.001  |  | Hosmer-Lemeshow Chi square=23.96, d.f.=8, P=0.002 |

E/O denotes expected number of breast cancer cases/observed number of cases

\*Predicted 2-year risk

†P<0.05 for test of the null hypothesis that E/O=1; ‡P<0.01 for test of the null hypothesis that E/O=1

Supplemental Table 5. Calibration of predictions from the Gail and Tyrer-Cuzick models in the Nurses’ Health Study: 1,575 incident breast cancer cases in 217,916 2-year intervals among women age 60-69 at the beginning of the interval

|  |  |  |  |
| --- | --- | --- | --- |
| Gail model | Gail model calibration | Tyrer-Cuzick model | Tyrer-Cuzick model calibration |
| Risk decile cutpoints | Intervals, expected and observed cases | Risk decile cutpoints | Intervals, expected and observed cases |
| Predicted risk (%)\* | N | E/O | Ratio, (95% CI) | Predicted risk (%)\* | N | E/O (ratio) | Ratio, (95% CI) |
| .0249-.2485 | 194 | 0.43/1 | 0.43, (0.06, 3.02) | .0258-.2644 | 142 | 0.34/1 | 0.34, (0.05, 2.44) |
| .2486-.3474 | 965 | 2.9/6 | 0.49, (0.22, 1.08) | .2644-.3604 | 2,210 | 7.3/9 | 0.81, (0.42, 1.55) |
| .3480-.4020 | 538 | 2.0/3 | 0.68, (0.22, 2.11) | .3604-.4262 | 6,806 | 27.2/19 | 1.43, (0.91, 2.24) |
| .4023-.4755 | 1,230 | 5.4/6 | 0.90, (0.40, 2.00) | .4262-.4837 | 13,032 | 59.6/46 | 1.30, (0.97, 1.73) |
| .4757-.5313 | 28,183 | 144.1/147 | 0.98, (0.83, 1.15) | .4837-.5428 | 19,935 | 102.7/76 | 1.35, (1.08, 1.69)‡ |
| .5314-.6097 | 39,992 | 234.9/230 | 1.02, (0.90, 1.16) | .5428-.6089 | 26,251 | 151.3/149 | 1.02, (0.86, 1.19) |
| .6098-.6902 | 34,754 | 227.0/215 | 1.06, (0.92, 1.21) | .6089-.6909 | 31,906 | 207.1/178  | 1.16, (1.00, 1.35)† |
| .6904-.8001 | 46,303 | 341.8/347 | 0.99, (0.89, 1.09) | .6909-.8101 | 36,994 | 276.3/270 | 1.02, (0.91, 1.15) |
| .8002-.9941 | 31,459 | 276.1/281 | 0.98, (0.87, 1.10) | .8101-1.042 | 40,620 | 369.2/378 | 0.98, (0.88, 1.08) |
| .9948-4.289 | 34,298 | 462.1/339 | 1.36, (1.23, 1.52)‡ | 1.042-5.141 | 40,020 | 591.4/449 | 1.32, (1.20, 1.44)‡ |
| Overall | 217,916 | 1,697/1,575 | 1.08, (1.03, 1.13)‡ |  | 217,916  | 1,792/1,575 | 1.14, (1.08, 1.20)‡ |
| Average (SD), min-max predicted risk (%) |  | 0.78 (0.31), 0.1771-4.284 |  | 0.82 (.39), .1758-4.284 |
|  | Hosmer-Lemeshow Chi square =38.31, d.f.=8, P<0.001  |  | Hosmer-Lemeshow Chi square=52.90, d.f.=8, P<0.001 |

E/O denotes expected number of breast cancer cases/observed number of cases

\*Predicted 2-year risk

†P<0.05 for test of the null hypothesis that E/O=1; ‡P<0.01 for test of the null hypothesis that E/O=1

Supplemental Table 6. Calibration of predictions from the Gail and Tyrer-Cuzick models in the Nurses’ Health Study: 752 incident breast cancer cases in 106,239 2-year intervals among women age 70 or older at the beginning of the interval

|  |  |  |  |
| --- | --- | --- | --- |
| Gail model | Gail model calibration | Tyrer-Cuzick model | Tyrer-Cuzick model calibration |
| Risk decile cutpoints | Intervals, expected and observed cases | Risk decile cutpoints | Intervals, expected and observed cases |
| Predicted risk (%)\* | N | E/O | Ratio, (95% CI) | Predicted risk (%)\* | N | E/O (ratio) | Ratio, (95% CI) |
| .0249-.2485 | 407 | 0.84/5 | 0.17, (0.07, 0.40)‡ | .0258-.2644 | 240 | 0.57/2 | 0.28, (0.07, 1.13) |
| .2486-.3474 | 224 | 0.65/0 | Undefined | .2644-.3604 | 2,348 | 7.7/9 | 0.85, (0.44, 1.64) |
| .3480-.4020 | 63 | 0.24/0 | Undefined | .3604-.4262 | 5,861 | 23.3/27 | 0.86, (0.59, 1.26) |
| .4023-.4755 | 256 | 1.13/1 | 1.13, (0.16, 8.05) | .4262-.4837 | 9,120 | 41.6/50 | 0.83, (0.63, 1.10) |
| .4757-.5313 | 314 | 1.60/1 | 1.60, (0.22, 11.33) | .4837-.5428 | 11,669 | 59.9/57 | 1.05, (0.81, 1.36) |
| .5314-.6097 | 5,017 | 29.5/28 | 1.05, (0.73, 1.52) | .5428-.6089 | 13,448 | 77.4/68 | 1.14, (0.90, 1.44) |
| .6098-.6902 | 16,765 | 109.1/84 | 1.30, (1.05, 1.61)† | .6089-.6909 | 14,458 | 93.8/91  | 1.03, (0.84, 1.27) |
| .6904-.8001 | 15,419 | 113.5/87 | 1.30, (1.06, 1.61)† | .6909-.8101 | 14,964 | 111.7/111 | 1.01, (0.84, 1.21) |
| .8002-.9941 | 34,635 | 294.8/245 | 1.20, (1.06, 1.36)‡ | .8101-1.042 | 15,401 | 140.1/137 | 1.02, (0.86, 1.21) |
| .9948-4.289 | 33,139 | 455.6/301 | 1.51, (1.35, 1.69)‡ | 1.042-5.141 | 18,730 | 279.3/200 | 1.40, (1.22, 1.60)‡ |
| Overall | 106,239 | 1,006.8/752 | 1.34, (1.25, 1.44)‡ |  | 106,239  | 835.4/752 | 1.11, (1.03, 1.19)‡ |
| Average (SD), min-max predicted risk (%) |  | 0.95 (0.38), 0.106-4.289 |  | 0.79 (.40), 0.148-5.141 |
|  | Hosmer-Lemeshow Chi square =94.74, d.f.=8, P<0.001  |  | Hosmer-Lemeshow Chi square=30.06, d.f.=8, P<0.001 |

E/O denotes expected number of breast cancer cases/observed number of cases

\*Predicted 2-year risk

†P<0.05 for test of the null hypothesis that E/O=1; ‡P<0.01 for test of the null hypothesis that E/O=1

Supplemental Table 7. Cross-classification of predicted and observed risk by the Gail model and the Tyrer-Cuzick model based on 616 incident breast cancer cases over 193,390 2-year intervals among women under age 50 at the beginning of the interval

|  |  |
| --- | --- |
|  | Tyrer-Cuzick model 2-yr risk |
| Gail model 2-yr risk | 0-<.4% | .4-<.67% | .67-<1.0% | ≥1.0% |
| 0-<.4%, n | **140,374** | 20,964 | 72 | 10 |
|  Cases (risk\*) | **365 (2.6)** | 88 (4.2) | 0 (0.0) | 0 (0.0) |
|  |  |  |  |  |
| .4-<.67%, n | 8,873 | **14,860** | 3,238 | 405 |
|  Cases (risk\*) | 36 (4.1) | **75 (5.0)** | 25 (7.7) | 3 (7.4) |
|  |  |  |  |  |
| .67-<1.0%, n | 245 | 1,072 | **1,596** | 630 |
|  Cases (risk\*) | 0 (0.0) | 7 (6.5) | **8 (5.0)** | 3 (4.8) |
|  |  |  |  |  |
| ≥1.0%, n | 0 | 140 | 642 | **269** |
|  Cases (risk\*) | 0 (0.0) | 0 (0.0) | 3 (4.7) | **3 (11.2)** |

\*2-year risk x 1,000

Net reclassification index (cases): Gail model: (36+7+3)/616 = 7.5%;

Tyrer-Cuzick model: (88+25+3)/616 = 18.8%

Net reclassification index (non-cases): Gail model: (20876+72+10+3213+402+627)/192774 = 13.1%;

Tyrer-Cuzick: (8837+245+1065+140+639)/192774 = 5.7%

Supplemental Table 8. Cross-classification of predicted and observed risk by the Gail model and the Tyrer-Cuzick model based on 1,441 incident breast cancer cases over 251,403 2-year intervals among women age 50-59 at the beginning of the interval

|  |  |
| --- | --- |
|  | Tyrer-Cuzick model 2-yr risk |
| Gail model 2-yr risk | 0-<.4% | .4-<.67% | .67-<1.0% | ≥1.0% |
| 0-<.4%, n | **19,861** | 40,441 | 1675 | 18 |
|  Cases (risk\*) | **63 (3.2)** | 158 (3.9) | 11 (6.6) | 0 (0.0) |
|  |  |  |  |  |
| .4-<.67%, n | 17,279 | **104,594** | 29,819 | 1,316 |
|  Cases (risk\*) | 61 (3.5) | **560 (5.4)** | 250 (8.4) | 12 (9.1) |
|  |  |  |  |  |
| .67-<1.0%, n | 200 | 5,359 | **11,102** | 11,180 |
|  Cases (risk\*) | 0 (0.0) | 37 (6.9) | **94 (8.5)** | 106 (9.5) |
|  |  |  |  |  |
| ≥1.0%, n | 0 | 99 | 1,580 | **6,880** |
|  Cases (risk\*) | 0 (0.0) | 0 (0.0) | 15 (9.5) | **74 (10.8)** |

\*2-year risk x 1,000

Net reclassification index (cases): Gail model: (61+37+15)/1441 = 7.8%;

Tyrer-Cuzick model: (158+11+250+12+106)/1441 = 37.3%

Net reclassification index (non-cases): Gail model: (40283+1664+18+29569+1304+11074)/249962 = 33.6%;

Tyrer-Cuzick: (17218+200+5322+99+1565)/249962 = 9.8%

Supplemental Table 9. Cross-classification of predicted and observed risk by the Gail model and the Tyrer-Cuzick model based on 1,575 incident breast cancer cases over 217,916 2-year intervals among women age 60-69 at the beginning of the interval

|  |  |
| --- | --- |
|  | Tyrer-Cuzick model 2-yr risk |
| Gail model 2-yr risk | 0-<.4% | .4-<.67% | .67-<1.0% | ≥1.0% |
| 0-<.4%, n | **105** | 889 | 611 | 87 |
|  Cases (risk\*) | **0 (0.0)** | 3 (3.4) | 6 (9.8) | 1 (11.5) |
|  |  |  |  |  |
| .4-<.67%, n | 4,518 | **57,435** | 36,677 | 4,494 |
|  Cases (risk\*) | 16 (3.5) | **254 (4.4)** | 253 (6.9) | 65 (14.5) |
|  |  |  |  |  |
| .67-<1.0%, n | 972 | 27,752 | **38,135** | 11,959 |
|  Cases (risk\*) | 3 (3.1) | 149 (5.4) | **339 (8.9)** | 147 (12.3) |
|  |  |  |  |  |
| ≥1.0%, n | 10 | 873 | 4,973 | **28,426** |
|  Cases (risk\*) | 0 (0.0) | 4 (4.6) | 33 (6.6) | **302 (10.6)** |

\*2-year risk x 1,000

Net reclassification index (cases): Gail model: (16+3+149+4+33)/1575 = 14.2%;

Tyrer-Cuzick model: (3+6+1+253+65+147)/1575 = 30.2%

Net reclassification index (non-cases): Gail model: (886+605+86+36424+4429+11812)/216341 = 25.1%;

Tyrer-Cuzick: (4502+969+27603+10+869+4940)/216341 = 18.0%

Supplemental Table 10. Cross-classification of predicted and observed risk by the Gail model and the Tyrer-Cuzick model based on 752 incident breast cancer cases over 106,239 2-year intervals among women age ≥70 at the beginning of the interval

|  |  |
| --- | --- |
|  | Tyrer-Cuzick model 2-yr risk |
| Gail model 2-yr risk | 0-<.4% | .4-<.67% | .67-<1.0% | ≥1.0% |
| 0-<.4%, n | **48** | 370 | 226 | 50 |
|  Cases (risk\*) | **0 (0.0)** | 3 (8.1) | 2 (8.8) | 0 (0.0) |
|  |  |  |  |  |
| .4-<.67%, n | 2,437 | **12,354** | 3,383 | 339 |
|  Cases (risk\*) | 14 (5.7) | **60 (4.9)** | 19 (5.6) | 0 (0.0) |
|  |  |  |  |  |
| .67-<1.0%, n | 2,855 | 30,856 | **19,202** | 3,311 |
|  Cases (risk\*) | 7 (2.5) | 170 (5.5) | **152 (7.9)** | 40 (12.1) |
|  |  |  |  |  |
| ≥1.0%, n | 130 | 4,701 | 8,996 | **16,981** |
|  Cases (risk\*) | 2 (15.4) | 21 (4.5) | 86 (9.6) | **176 (10.4)** |

\*2-year risk x 1,000

Net reclassification index (cases): Gail model: (14+7+170+2+21+86)/752 = 39.9%;

Tyrer-Cuzick model: (3+2+19+40)/752 = 8.5%

Net reclassification index (non-cases): Gail model: (367+224+50+3364+339+3271)/105487 = 7.2%;

Tyrer-Cuzick: (2423+2848+30686+128+4680+8910)/105487 = 47.1%

Supplemental Table 11. Calibration of predictions from the Gail and Tyrer-Cuzick models in the Nurses’ Health Study: 765 incident breast cancer cases in 86,892 2-year intervals among women with a family history (first degree relative) of breast cancer at the beginning of the interval

|  |  |  |  |
| --- | --- | --- | --- |
| Gail model | Gail model calibration | Tyrer-Cuzick model | Tyrer-Cuzick model calibration |
| Risk decile cutpoints | Intervals, expected and observed cases | Risk decile cutpoints | Intervals, expected and observed cases |
| Predicted risk (%)\* | N | E/O | Ratio, (95% CI) | Predicted risk (%)\* | N | E/O (ratio) | Ratio, (95% CI) |
| .0249-.2485 | 1,126 | 2.43/3 | 0.81, (0.26, 2.51) | .0258-.2644 | 536 | 1.14/2 | 0.57, (0.14, 2.28) |
| .2486-.3474 | 542 | 1.65/1 | 1.65, (0.23, 11.7)  | .2644-.3604 | 857 | 2.71/1 | 2.71, (0.38, 19.2) |
| .3480-.4020 | 401 | 1.53/0 | Undefined | .3604-.4262 | 824 | 3.25/2 | 1.63, (0.41, 6.50) |
| .4023-.4755 | 2,199 | 9.66/8 | 1.21, (0.60, 2.42) | .4262-.4837 | 896 | 4.09/2 | 2.04, (0.51, 8.17) |
| .4757-.5313 | 532 | 2.61/1 | 2.61, (0.37, 18.5) | .4837-.5428 | 1,086 | 5.58/1 | 5.58, (0.79, 39.6) |
| .5314-.6097 | 1,807 | 10.31/17 | 0.61, (0.38, 0.98)† | .5428-.6089 | 1,549 | 8.93/11 | 0.81, (0.45, 1.47) |
| .6098-.6902 | 3,890 | 25.26/26 | 0.97, (1.66, 1.43) | .6089-.6909 | 2,377 | 15.5/17 | 0.91, (0.57, 1.47) |
| .6904-.8001 | 7,497 | 55.55/46 | 1.21, (0.90, 1.61) | .6909-.8101 | 4,958 | 37.4/29  | 1.29, (0.90, 1.86) |
| .8002-.9941 | 12,549 | 113.1/113 | 1.00, (0.83, 1.20) | .8101-1.042 | 15,618 | 145.9/105 | 1.39, (1.15, 1.68)‡ |
| .9948-4.289 | 56,349 | 806.8/550 | 1.47, (1.35, 1.59)‡ | 1.042-5.141 | 58,191 | 894.3/595 | 1.50, (1.39, 1.63)‡ |
| Overall | 86,892 | 1,028.9/765 | 1.34, (1.25, 1.44)‡ |  | 86,892  | 1,118.8/765 | 1.46, (1.36, 1.57)‡ |
| Average (SD), min-max predicted risk (%) |  | 1.18 (0.48), 0.083-4.289 |  | 1.29 (.50), 0.120-5.141 |
|  | Hosmer-Lemeshow Chi square =90.96, d.f.=8, P<0.001  |  | Hosmer-Lemeshow Chi square=121.20, d.f.=8, P<0.001 |

E/O denotes expected number of breast cancer cases/observed number of cases

\*Predicted 2-year risk

†P<0.05 for test of the null hypothesis that E/O=1; ‡P<0.01 for test of the null hypothesis that E/O=1

Supplemental Table 12: Comparison of age-specific, and weighted averages of age-specific C-statistics for the Gail and Tyrer-Cuzick breast cancer prediction models in the Nurses’ Health Study: 765 incident breast cancer cases in 86,892 2-year intervals among women with a family history (first degree relative) of breast cancer at the beginning of the interval

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Cases | Gail model | Tyrer-Cuzick model | Difference |
| Age group | N | C ±SE | C ±SE | C ±SE, P-value |
| <50 years | 70 | .579±.034 | .597±.034 | .018±.025, 0.47 |
| 50-59 years | 236 | .564±.019 | .592±.018 | .028±.021, 0.18 |
| 60-69 years | 298 | .524±.017 | .558±.017 | .034±.021, 0.10 |
| ≥70 years | 161 | .548±.023 | .609±.022 | .062±.027, 0.02 |
| Weighted average† | 765 | .547±.010 | .583 ±.010 | .034±.011, 0.002 |
| Overall‡ | 765 | .556±.010 | .594±.010 | .039±.009, <0.001 |

†Weighted average of the age-group specific C-statistic

‡Based on prediction in all women with a family history without age adjustment

Supplemental Table 13. Cross-classification of predicted and observed risk by the Gail model and the Tyrer-Cuzick model based on 765 incident breast cancer cases in 86,892 2-year intervals among women with a family history (first degree relative) of breast cancer at the beginning of the interval

|  |  |
| --- | --- |
|  | Tyrer-Cuzick model 2-yr risk |
| Gail model 2-yr risk | 0-<.4% | .4-<.67% | .67-<1.0% | ≥1.0% |
| 0-<.4%, n | **1,510** | 516 | 21 | 20 |
|  Cases (risk\*) | **3 (2.0)** | 1 (1.9) | 0 (0.0) | 0 (0.0) |
|  |  |  |  |  |
| .4-<.67%, n | 313 | **3,451** | 3,163 | 759 |
|  Cases (risk\*) | 0 (0.0) | **17 (4.9)** | 26 (8.2) | 6 (7.9) |
|  |  |  |  |  |
| .67-<1.0%, n | 41 | 1,044 | **7,983** | 11,789 |
|  Cases (risk\*) | 0 (0.0) | 6 (5.7) | **47 (5.9)** | 109 (9.2) |
|  |  |  |  |  |
| ≥1.0%, n | 6 | 593 | 6,803 | **48,930** |
|  Cases (risk\*) | 1 (166.7) | 4 (6.7) | 42 (6.2) | **503 (10.3)** |

\*2-year risk x 1,000

Net reclassification index (cases): Gail model: (6+1+4+42)/765 = 6.9%;

Tyrer-Cuzick model: (1+26+6+109)/765 = 18.6%

Net reclassification index (non-cases): Gail model: (515+21+20+3137+753+11680)/86127 = 18.7%;

Tyrer-Cuzick: (313+41+1038+5+589+6761)/86127 = 10.2%

Supplemental Figure 1a. Scatterplot of observed versus expected counts over deciles of risk based on the Gail model with 45 degree line: subgroup of women with a family history of breast cancer in a first degree relative\*



\*higl and logl denote the upper and lower 95% confidence interval limits for the observed count

Supplemental Figure 1b. Scatterplot of observed versus expected counts over deciles of risk based on the Tyrer-Cuzick model with 45 degree line: subgroup of women with a family history of breast cancer in a first degree relative\*



\*hitc and lotc denote the upper and lower 95% confidence interval limits for the observed count