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Prediction of Breast Cancer Risk Based on Profiling With Common Genetic Variants

Nasim Mavaddat, Paul D. P. Pharoah, Kyriaki Michailidou, Jonathan Tyer, Mark N. Brook, Manjeet K. Bolla, Qin Wang, Joe Dennis, Alison M. Dunning, Mitul Shah, Robert Luben, Judith Brown, Stig E. Bojesen, Berge G. Nordestgaard, Sune F. Nielsen, Henrik Flyger, Kamila Czene, Hafere Darabi, Mikael Eriksson, Julian Peto, Isabel dos-Santos-Silva, Frank Dudbridge, Nichola Johnson, Marjanka J. Schmidt, Annegien Broeks, Senno Verhoef, Emiel J. Rutgers, Anthony Swedlow, Alan Ashworth, Nick Orr, Minouk J. Schoemaker, Jonine Figueroa, Stephen J. Chanock, Louise Brinton, Jolanta Lissowska, Fergus J. Couch, Janet E. Olson, Celine Vachon, Vernon S. Pankratz, Diether Lambrechts, Hans Wildiers, Chantal Van Ongeval, Erik Van Limbergen, Vessela Kristensen, Grethe Grenaker Alnæs, Silje Nord, Anne-Lise Borresen-Dale, Heli Nevanlinna, Taru A. Muranen, Kristiina Aittomäki, Carl Blomqvist, Jenny Chang-Claude, Anja Rudolph, Petra Seibold, Dieter Flesch-Jansys, Peter A. Fasching, Lothar Haeberle, Arif B. Ekici, Matthias W. Beckmann, Barbara Burwinkel, Frederik Marine, Andreas Schneeweiss, Christof Sohn, Amy Trentham-Dietz, Polly Newcomb, Linda Titus, Kathleen M. Egan, David J. Hunter, Sara Lindstrom, Ruella M. Tamimi, Peter Kraft, Nazneen Rahman, Clare Turnbull, Anthony Renwick, Sheila Seal, Jingmei Li, Jianjun Liu, Keith Humphreys, Javier Benitez, M. Pilar Zamora, Jose Ignacio Arias Perez, Primitiva Menendez, Anna Jakowowska, Jan Lubinski, Katarzyna Jaworska-Bieniek, Katarzyna Durda, Natalia V. Bogdanova, Natalia N. Antonenkova, Thilo Dörk, Hoda Anton-Culver, Susan L. Neuhausen, Argyrios Zagiouas, Leslie Bernstein, Peter Devilee, Robert A. E. M. Tollenaar, Caroline Seynaeve, Christi J. van Asperen, Angela Cox, Simon S. Cross, Malcolm W. R. Reed, Elza Khusnuddinova, Marina Bermisheva, Darya Prokofyeva, Zlatia Takihirova, Alfons Meindl, Rita K. Schmutzler, Christian Sutter, Rongxi Yang, Peter Schüermann, Michael Bremer, Hans Christiansen, Tjoung-Won Park-Simon, Peter Hilleman, Pascal Guénel, Thérèse Truong, Florence Menegaux, Marie Sanchez, Paolo Radice, Paolo Peterlongo, Siranoush Manoukian, Valeria Pensotti, John L. Hopper, Helen Tsimiklis, Carmel Apicella, Melissa C. Southey, Hiltrud Brauch, Thomas Brüning, Yon-Dschun Ko, Alice J. Sigurdson, Michele M. Doody, Ute Hamann, Diana Torres, Hans-Ulrich Ulmer, Asta Förstl, Elinor J. Sawyer, Ian Tomlinson, Michael J. Kerin, Nicola Miller, Irene L. Andrulis, Julia A. Knight, Gerd Glendon, Anna Marie Mulligan, Georgia Chenevix-Trench, Rosemary Balleine, Graham G. Giles, Roger L. Milne, Catriona McLean, Annika Lindblom, Sara Margolin, Christopher A. Haiman, Brian E. Henderson, Fredrick Schumacher, Loic Le Marchand, Ursula Eibler, Shan Wang-Gohoke, Maartje J. Hooning, Antoinette Hollestelle, Ans M. W. van den Ouweland, Linetta B. Koppert, Jane Carpenter, Christine Clarke, Rodney Scott, Arto Mannnermaa, Vesa Katala, Veli-Matti Kosma, Jana M. Hartikainen, Hermann Brenner, Volker Arndt, Christa Stegmaier, Aida Karina Dieffenbach, Robert Winqvist, Katri Pylkäs, Arja Jukkola-Vuorinen, Mervi Grip, Kenneth Offit, Joseph Vijai, Mark Robson, Rohini Rau-Murthy, Miriam Dwek, Ruth Swann, Katherine Annie Perkins, Mark S. Goldberg, France Labrèche, Martine Dumont, Diana M. Eccles, William J. Tapper, Sajjad Rafiq, Esther M. John, Alice S. Whittemore, Susan Slager, Dakouris Yannoukakos, Amanda E. Toland, Song Yao, Wei Zheng, Sandra L. Halverson, Anna Gonzalez-Neira, Guillermo Pita, M. Rosario Alonso, Nuria Álavan, Daniel Herrera, Daniel C. Tesser*, Daniel Vincent, Francois Bacot, Craig Luccarini,
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Abstract

Background: Data for multiple common susceptibility alleles for breast cancer may be combined to identify women at different levels of breast cancer risk. Such stratification could guide preventive and screening strategies. However, empirical evidence for genetic risk stratification is lacking.

Methods: We investigated the value of using 77 breast cancer-associated single nucleotide polymorphisms (SNPs) for risk stratification, in a study of 33,673 breast cancer cases and 33,381 control women of European origin. We tested all possible pair-wise multiplicative interactions and constructed a 77-SNP polygenic risk score (PRS) for breast cancer overall and by estrogen receptor (ER) status. Absolute risks of breast cancer by PRS were derived from relative risk estimates and UK incidence and mortality rates.

Results: There was no strong evidence for departure from a multiplicative model for any SNP pair. Women in the highest 1% of the PRS had a three-fold increased risk of developing breast cancer compared with women in the middle quintile (odds ratio [OR] = 3.36, 95% confidence interval [CI] = 2.95 to 3.83). The ORs for ER-positive and ER-negative disease were 3.73 (95% CI = 3.24 to 4.30) and 2.80 (95% CI = 2.26 to 3.46), respectively. Lifetime risk of breast cancer for women in the lowest and highest quintiles of the PRS was 5.2% and 16.6% for a woman without family history, and 8.6% and 24.4% for a woman with a first-degree family history of breast cancer.

Conclusions: The PRS stratifies breast cancer risk in women both with and without a family history of breast cancer. The observed level of risk discrimination could inform targeted screening and prevention strategies. Further discrimination may be achievable through combining the PRS with lifestyle/environmental factors, although these were not considered in this report.
effects of the 77 SNPs on overall breast cancer risk, as well as on the risk of ER-positive and ER-negative disease separately. We estimated absolute risks of developing breast cancer for different levels of the PRS, accounting for the competing risk of mortality from other causes. Effect sizes were confirmed in one large study (pKARMA) that was not part of any SNP discovery set. We discuss the degree of breast cancer risk stratification obtained in women with and without a family history of breast cancer.

Methods

Study Subjects and Genotyping

Study participants for the primary analyses (set 1) were 89,049 women of European origin participating in 41 studies in BCAC. All studies were approved by the relevant institutional review boards, and all individuals gave written informed consent. Samples were genotyped using a custom Illumina iSelect array (iCOGS) comprising 211,155 SNPs (15). For some analyses, a further 72,014 women in BCAC genotyped for the relevant SNPs in earlier experiments were included (set 2). For PRS analyses (67,054 women), studies that oversampled breast cancer cases with a family history (21,995 women) were excluded. Supplementary Tables 1–3 (available online) show study designs and numbers of breast cancer cases and control women included.

Analyses were based primarily on variants reported to be associated (at \( P < 5 \times 10^{-8} \)) by COGS or previous publications, with either breast cancer overall or ER-negative disease. SNPs and regions included are summarized in Supplementary Table 4 (available online).

Statistical Methods

Tests for pair-wise SNP*SNP interactions (departures from a multiplicative model) were carried out using logistic regression, with breast cancer as the outcome. The two SNPs were each coded as a categorical variable (ie, fitting a separate parameter for heterozygous and risk-allele homozygous genotypes), while the interaction term (SNP1*SNP2) was included as continuous covariate. All analyses were adjusted for study and seven principal components (PC) to account for population substructure.

Results

Pairwise Multiplicative SNP*SNP Interaction Analyses

Data on 46,450 breast cancer cases and 42,599 controls from 41 studies were included in the interaction analyses.
(Supplementary Table 3, available online). There was no strong evidence for interaction between any particular SNP pair after Bonferroni correction (Supplementary Tables 5–6, available online). Plots of expected vs observed log_{10} P values for SNP*SNP interaction tests showed slight departure from the null hypothesis of multiplicative effects (Supplementary Figure 1, A and B, available online), and the number of statistically significant interactions with P_{interaction} values of less than .01 was larger than expected by chance (Table 1). To investigate whether there was an excess of synergistic or antagonistic interactions, the direction of the interaction term relative to the main effects was examined for SNP pairs with P_{interaction} values of less than .01. For case-control analyses, 47% of interactions were synergistic and 53% antagonistic, and for case-only analyses 53% were synergistic and 46% antagonistic. These proportions were not statistically significantly different from the null expectation (P > .05). Meta-analysis of SNP*SNP interaction test results from the iCOGS dataset with those from 72 014 additional women in BCAC yielded similar results (Supplementary Table 7, available online). Given that no SNP pair showed strong evidence for departure from the multiplicative model, subsequent analyses were based on a PRS that included the main effects of SNPs but no SNP*SNP interaction terms.

### Association Between PRS and Breast Cancer Risk

As predicted by the polygenic, multiplicative model, the number of breast cancer risk alleles and the 77-SNP PRS approximated a normal distribution for both breast cancer cases and control women (Figure 1). The odds ratios for developing breast cancer by percentiles of the PRS, compared with women in the middle quintile (40th to 60th percentile) are shown in Figure 2A. The observed odds ratios were similar to the odds ratios predicted under a polygenic multiplicative model; the 95% confidence interval (CI) included the predicted odds ratio at all points except the 80th to 90th percentile (Figure 2A; Supplementary Table 8, available online). For women in the lowest 1% of the PRS distribution, the estimated odds ratio compared with women in the middle quintile was 0.32 (95% CI = 0.25 to 0.40). By contrast, for women in the highest 1% of the PRS distribution, the estimated OR compared with women in the middle quintile was 3.36 (95% CI = 2.95 to 3.83, P = 7.5x10^{-74}). When PRS were derived separately for ER-positive and ER-negative disease, the corresponding odds ratios were 3.73 (95% CI = 3.24 to 4.30) and 2.80 (95% CI = 2.26 to 3.46), respectively (Figure 2, B and C). The log OR per unit standard deviation of the PRS was 0.44 (95% CI = 0.42 to 0.46) for overall breast cancer, 0.49 (95% CI = 0.47 to 0.51) for ER-positive, and 0.37 (95% CI = 0.34 to 0.40) for ER-negative disease (Table 3). A validation analysis including only one large study (pKARMA) that was not part of any SNP discovery analyses found similar odds ratio estimates to those in the remaining studies, except for the 60% to 80% and 90% to 95% categories, for which estimates were higher in pKARMA (Table 4; Supplementary Table 9, available online). The log OR per unit SD was also similar for pKARMA alone (log OR per unit SD = 0.4).

The associations between PRS and breast cancer in different age groups are summarized in Table 3 and Supplementary Figure 2 (available online). There was a statistically significant interaction between PRS and age, the association between PRS and breast cancer risk decreasing with age (Table 3).

A family history of breast cancer in one or more affected first-degree relatives was reported by 18.5% of breast cancer cases and 11.1% of control women. The odds ratio for family history was attenuated from 1.81 to 1.68 (12.6% attenuation) after adjusting for the PRS (Table 2). At younger ages (<40 years), there was less attenuation (from 2.90 to 2.76, 4.6% attenuation) (Table 2). The joint effects of the PRS and family history were largely consistent with a multiplicative model (P_{interaction} = .34 for the interaction between the PRS and family history; data not shown); however, we observed a stronger effect of family history for women at the lowest 1% of the PRS (Supplementary Table 10, available online). The discriminative accuracy of the PRS, as measured by the C-statistic, was 0.622 (95% CI = 0.619 to 0.627); discrimination was

### Table 2. Odds ratio for family history of breast cancer in first-degree relatives: unadjusted and adjusted by PRS and stratified by age

| Age group | Unadjusted by PRS | Adjusted by PRS |
|-----------|-------------------|-----------------|
| All subjects | 1.81 (1.69 to 1.93) | 1.68 (1.56 to 2.86) | 12.6% |
| <40 y | 2.90 (2.07 to 4.07) | 2.76 (1.96 to 3.89) | 4.6% |
| 40–60 y | 1.88 (1.71 to 2.08) | 1.72 (1.56 to 1.90) | 14.1% |
| ≥60 y | 1.63 (1.47 to 1.82) | 1.53 (1.37 to 1.70) | 13.0% |

* Odds ratio for developing breast cancer for women with a family history of breast cancer in a first-degree relative compared with women without a family history; adjusting for study and seven principal components. 21 865 breast cancer cases and 15 830 control women provided family history information. CI = confidence intervals; PRS = polygenic risk score; OR = odds ratio.
† Percent attenuation on log scale.

### Table 3. Association between PRS and breast cancer risk in different age groups

| Age group | All breast cancers | ER-positive disease | ER-negative disease |
|-----------|--------------------|---------------------|---------------------|
|          | log OR (95% CI)    | log OR (95% CI)     | log OR (95% CI)     |
| All ages | 0.44 (0.42 to 0.46) | 0.49 (0.47 to 0.51) | 0.37 (0.34 to 0.40) |
| <40 y    | 0.46 (0.38 to 0.53) | 0.56 (0.47 to 0.65) | 0.48 (0.36 to 0.59) |
| 40–60 y  | 0.46 (0.42 to 0.50) | 0.53 (0.48 to 0.57) | 0.36 (0.29 to 0.43) |
| 50–59 y  | 0.48 (0.45 to 0.51) | 0.54 (0.50 to 0.57) | 0.37 (0.32 to 0.43) |
| ≥60 y    | 0.41 (0.38 to 0.43) | 0.44 (0.41 to 0.47) | 0.36 (0.31 to 0.42) |
| Interaction between PRS and age | Interaction OR (95% CI) | Interaction OR (95% CI) | Interaction OR (95% CI) |
| P_{interaction} | .005 | 1.08x10^{-4} | .006 |

* Age of breast cancer cases (age at diagnosis) and control women (age at interview). CI = confidence intervals; PRS = polygenic risk score; log OR = log odds ratio.
† log OR for association between the PRS coded as a continuous variable and breast cancer risk (per unit SD of the PRS)
‡ OR per 10 years for interaction between PRS and age.
similar when restricted to pKARMA alone, with an area under the curve of 0.615 (95% CI = 0.608 to 0.616) (data not shown).

Absolute Risks of Developing Breast Cancer by Levels of PRS

The estimated risk of developing breast cancer by age 80 years for women in the lowest and highest 1% of the PRS was 3.5% (95% CI = 2.6% to 4.4%) and 29.0% (95% CI = 24.9% to 33.5%), respectively (Figure 3A). For the lowest and highest quintiles of the PRS, the risk was 5.3% (95% CI = 5.1% to 5.7%) and 17.2% (95% CI = 16.1% to 18.1%), respectively (data not shown). The corresponding risks of developing ER-positive disease were 4.1% and 15.7% for women in the lowest and highest quintiles, respectively, of the ER-positive PRS (averaged over all ER-negative PRS categories), whereas the highest lifetime risk for ER-negative disease was 2.4% (women in the highest quintile of ER-negative PRS and average ER-positive risk) (Figure 3). Lifetime risk of breast cancer for women in the lowest and highest quintiles of the PRS were 5.2% and 16.6% for a woman without family history and 8.6% and 24.4% for a woman with a first-degree family history of breast cancer (Figure 4).

We estimated the 10-year absolute risk of breast cancer at different ages and evaluated the age at which women at different levels of the PRS reach a threshold of 2.4%, which corresponds to the average 10-year risk of breast cancer for women age 47 years. This threshold was reached at 32 years for women whose PRS is above the 99th percentile of the PRS, and 57 years for women in the 20th to 40th percentiles of the PRS, and was never reached for women in lower percentiles (Figure 3D). As expected, lifetime risks were higher, and the ages at which the 2.4% threshold was reached were lower for women with a family history of breast cancer (Figure 4).

Discussion

In this report, we evaluated the degree of breast cancer risk stratification that can be attained in women of European ancestry using data for 77 common genetic variants, summarized as a PRS. Our results show that the PRS stratifies breast cancer risk in women without family history and refines genetic risk in women with a family history of breast cancer.

The PRS we used (sum of the minor alleles weighted by the per-allele log OR) is the most efficient, assuming that SNP odds ratios combine multiplicatively (i.e., no interactions on a log-additive scale) (18). Evaluation of pairwise SNP interactions showed that this was a reasonable assumption. Although no individual interactions could be established, we observed an excess of multiplicative interactions at P less than .01. This could be the result of underlying population stratification not accounted for by principal components adjustment or reflect the presence of multiple interactions too weak to be established individually. A recent study also found no evidence for interactions among SNPs with weaker evidence for main effects (19). Although we did not test for higher order interactions among SNPs, consistency between empirical and predicted odds ratios assuming multiplicative effects suggests that across all possible multifactor interactions the overall effect is close to multiplicative.

The 77-SNP PRS was associated with a larger effect than previously reported for a 10-SNP PRS (20). For example, our odds ratio for breast cancer for women in the highest compared with the middle quintile was 1.82 (95% CI = 1.73 to 1.90) vs 1.44 (95% CI = 1.35 to 1.53) for the 10-SNP PRS (20). A potential concern is that the PRS was constructed using iCOGS data that were, in part, the basis for discovery of many of the loci. This could lead to some upward bias in the odds ratio estimates (winner’s curse); however, analyses based on a large study (pKARMA) that was not part of any discovery set obtained similar estimates indicating that any winner’s curse effect is likely to be small.

There has been little evidence of differences by age in the per-allele odds ratio for individual SNPs. However, we observed a small but statistically significant decrease in odds ratio for PRS with increasing age. As expected, the odds ratio for family history was reduced after adjustment for the PRS. This attenuation (~12.6%) was consistent with the estimated fraction of the two-fold FRR explained by the 77-SNPs under a polygenic risk model (15). The joint effects of PRS and family history were consistent with a multiplicative model. A stronger FRR was observed for women at the lowest percentile of the PRS, but this was based on small numbers and requires confirmation. The degree of attenuation of the family history odds ratio was lower below age 40 years, as a result of the higher FRR at young ages, suggesting that rarer genetic variants may be more important at young ages.

We calculated the absolute risk of developing breast cancer for women at different levels of genetic risk according to the PRS. The lifetime risk for women below the first and above the 99th percentile of the PRS was 3.5% (95% CI = 2.6% to 4.4%) and 29.0% (95% CI = 24.9% to 33.5%), respectively. UK NICE guidelines recommend enhanced surveillance for women with a family history with lifetime risk of developing breast cancer over 17% (21). Figure 3 indicates that the PRS alone could identify approximately 8% of all women in the UK population at this level of risk, regardless of family history or other risk factors; approximately 17% of all breast cancer cases in the population would be expected to occur among these women. By contrast, the low absolute risk of breast cancer among women at the lowest end of the risk distribution raises the possibility that such women might be recommended more limited surveillance. Women at different levels of the PRS reach the same 10-year risk threshold at different ages, supporting the notion that using SNP profiles rather than age alone as a criterion to offer routine mammographic screening could lead to more effective screening programs (6). The utility of such an approach...
Prediction of subtype-specific breast cancer should also be informative for prevention (4). Recently updated NICE guidelines include recommendations to use endocrine treatments (tamoxifen and raloxifene) for primary prevention of breast cancer for women at moderate to high risk (21). These guidelines are based on risk of overall breast cancer for women with a family history of breast cancer. However, because these drugs prevent only ER-positive tumours, risk estimates incorporating the ER-positive PRS could better define the subset of women most likely to benefit. Our sample was derived from studies in Europe, North America, and Australia and restricted to women of European origin. While the results should be widely applicable in these populations, additional studies will be required to develop and validate genetic profiles for other populations, in particular Asian and African populations, where SNP associations, background incidence rates and distribution of tumour characteristics are substantially different.

Our analysis summarized family history in terms of a single binary variable, but familial risk of breast cancer also depends on the number of affected and unaffected relatives and their ages. Risk prediction algorithms that combine full family history data with a polygenic component perform better than simpler models (22). It is possible to incorporate the current PRS into family-history based models for breast cancer, such as BOADICEA, to improve genetic risk prediction (23).

Figure 1. Distribution of the number of breast cancer risk alleles (A) and polygenic risk score residuals after adjusting the polygenic risk score (PRS) for study and seven principal components (B), in 33,673 breast cancer cases and 33,381 control women of European origin. The PRS approximated a normal distribution in both breast cancer cases and control women. The mean PRS was 0.69 for breast cancer cases and 0.49 for control women. PRS residuals are standardized Pearson’s residuals calculated after regression of the score on seven principal components.
Figure 2. Association between the polygenic risk score (PRS) and breast cancer risk in women of European origin for (A) all breast cancers, (B) estrogen receptor (ER)-positive disease, and (C) ER-negative disease. Odds ratios are for different percentiles of the PRS relative to the middle quintile (40% to 60%) of the PRS. Odds ratios and 95% confidence intervals are shown. Regular lines denote the observed estimates, and dotted lines the theoretical estimates under a multiplicative polygenic model with a standard deviation of the PRS of 0.45 for all breast cancer, 0.50 for ER-positive breast cancer, and 0.38 for ER-negative breast cancer, as derived from the estimated effect sizes and allele frequencies/haplotype frequencies for each locus. PRS = polygenic risk score.
statistical significance, together with variants in genes conferring intermediate or high risk (15).

The risk discrimination provided by the genetic profile, summarised in the PRS and family history, should be further improved by combining, with lifestyle risk factors, benign breast disease, and mammographic density (24,25,28). Although we did not consider lifestyle factors explicitly in this dataset, other large studies have found no good evidence for interactions between common susceptibility SNPs and lifestyle factors for breast cancer, suggesting that SNPs generally combined multiplicatively (26,27). Darabi et al. (25) estimated a C-statistic of 0.60 for lifestyle risk factors including mammographic density. By comparison, we estimated the C-statistic for the PRS to be 0.62. Assuming that the multiplicative model is correct, the C-statistic would increase to 0.66 with the addition of the lifestyle risk factors. If modifiable risk factors and the PRS act multiplicatively, targeting public health interventions to women at higher genetic risk should result in a larger absolute risk reduction. For example, the decision to prescribe hormone replacement therapy might be guided by the PRS (28). Similar considerations would apply to risk-reducing interventions such as preventive medication and oophorectomy.

Some limitations of this study should be noted. Although the study was extremely large, the numbers of breast cancer cases and control women were still too limited to provide precise estimates of relative risks in the extremes of the PRS (for example, the highest 1%). Numbers were also limited to explore the effects at very young ages, and estimates were less precise for ER-negative disease. There was heterogeneity among the studies, both in population and design, but we saw no evidence of heterogeneity in SNP odds ratios among studies, suggesting that the estimates should be broadly applicable. Oversampling for family history could have led to a bias in the odds ratios by PRS, and for this reason we excluded studies that were sampled on the basis of family history. Finally, we were not able to consider lifestyle/environmental risk factors in our model, as data on all of these risk factors were not consistently available across all studies. Interactions between the PRS and environmental factors will need to be explicitly tested for in future studies.

In previous reports, improvement in risk discrimination by genomic profiling over that conferred by known risk factors was not substantial (24,29), although better discrimination was obtained for certain subgroups of women (30,31). Previous analyses, however, were based on a much smaller set of SNPs than included in this report. This study provides precise empirical estimates of the combined effects of multiple SNPs and the level of risk stratification possible. These estimates may inform the debate on public health utility and implementation of the PRS in clinical practice. Our work suggests that the PRS, particularly when used in combination with other risk factors, could help identify subsets of women at different levels of risk, for whom management would differ. The PRS may facilitate early detection of cancers in younger women and, importantly, identify individuals at risk of specific subtypes of breast cancer. Finally, there is potential for a stronger impact in modifying environmental factors in women at higher risk of breast cancer. Prospective analyses of the 77 SNP PRS, in combination with other risk factors, will be required to validate the overall accuracy of risk prediction. Such a comprehensive risk prediction
algorithm could provide a powerful basis for stratified breast cancer prevention programs.

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