Supplementary methods S1

Polygenic risk scores

Each PRS was calculated using published estimates (1, 2) of the odds ratio (OR) per effect allele and effect allele frequency (p), assuming independent and additive risks on the logOR scale (3, 4). For each SNP, the unscaled population average risk (μ) was calculated as:

$$\mu = (1-p)^2 + 2p(1-p)OR + p^2OR^2$$

Next, adjusted risks (which have a population average risk equal to 1) for each SNP were calculated as:

$$adjusted\_risk = \frac{OR^N}{\mu}$$

where N is the number of effect alleles. Any participants who were missing genotype data for one or more SNPs were given an adjusted risk of 1 for each missing SNP.

The overall PRS was then the product of the adjusted risk values for each of the SNPs.

Risk modifier score

First, calculate a risk modifier score (*risk_mod*) for each woman:

$$\begin{aligned}\ln(risk\_mod) &= \ln(snprisk) \times 1.03 \\ &+ \ln(fh\_risk) \\ &+ -0.04 + ((\ln(bmi/5) - 1.62) \times -0.35) \text{ if } menopausal\_status=0 \\ &+ 0.05 + ((\ln(bmi/5) - 1.62) \times 0.88) \text{ if } menopausal\_status=1\end{aligned}$$

then:

$$risk\_mod = e^{\ln(risk\_mod)}$$

5-year and full-lifetime risks

The calculation of 5-year and full-lifetime risks used annual, age-specific and age-standardized population incidences for women from England (5). For the 5-year risks, we

applied the competing mortality adjustment in equation 5 of Gail et al (6) using annual sex- and age-specific non-breast cancer mortality rates from England and Wales (7, 8). These incidences and mortality rates are annual and constant in 5- or 10-year periods, so as in equation 6 of Gail et al (6), they reduce to the following explicit formulae.

Let $\lambda_1(t)$ be the risk modifier score from the previous section multiplied by the population breast cancer incidences (above) for a woman aged t years. Let $\lambda_2(t)$ be the non-breast cancer mortality rates (above) for a woman aged t years. Assume $\lambda_1(t)$ is a step function of t which is constant for t in all intervals of the form $[k,\ k+1)$ for an integer k (this holds true for our incidences and rates, in fact they are constant in larger, 5- or 10-year, intervals). This is the same assumption as in Gail et al (6) with $\tau_j = j+1$ and $\Delta_j = 1$, in their terminology. Then equation 6 of Gail et al (6) says that the probability that a woman will develop breast cancer in the next 5 years, given that she is currently unaffected and aged a years, is the 5-year risk

$$\sum_{j=a}^{a+4} \frac{\lambda_1(j)}{\lambda_1(j)+\lambda_2(j)} \frac{S_1(j)}{S_1(a)} \frac{S_2(j)}{S_2(a)} [1-\exp(-\lambda_1(j)-\lambda_2(j))],$$

where

$$S_1(t) = \exp(-\lambda_1(0)-\lambda_1(1)-\lambda_1(2)-\cdots-\lambda_1(t-1))$$

if $t \geq 1$ is an integer, and $S_2(t)$ has the same definition except with a subscript of 2 instead of 1.

We calculated the full lifetime breast cancer risks using the equations above for ages $j = 0$ to $j = 84$.

Supplementary references

1. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet. 2019;104(1):21-34.
2. Mavaddat N, Pharoah PD, Michailidou K, Tyrer J, Brook MN, Bolla MK, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107(5).
3. Mealiffe ME, Stokowski RP, Rhees BK, Prentice RL, Pettinger M, Hinds DA. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. J Natl Cancer Inst. 2010;102(21):1618-27.
4. Dite GS, MacInnis RJ, Bickerstaffe A, Dowty JG, Allman R, Apicella C, et al. Breast cancer risk prediction using clinical models and 77 independent risk-associated SNPs for women aged under 50 years: Australian Breast Cancer Family Registry. Cancer Epidemiol Biomarkers Prev. 2016;25(2):359-65.
5. Office for National Statistics. Cancer registration statistics 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.
6. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879-86.

7. Office of National Statistics. Mortality statistics - underlying cause, sex and age 2019 [Available from: https://www.nomisweb.co.uk/query/construct/summary.asp?mode=construct&version=0&dataset=161.

8. Office of National Statistics. Mortality statistics 2016 [Available from: https://www.nomisweb.co.uk/query/construct/summary.asp?mode=construct&version=0&dataset=161.