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ORIGINAL ARTICLE

Estimation of age of onset and progression of breast cancer by absolute risk dependent on polygenic risk score and other risk factors

Rikesh Bhatt PhD[1] | Ardo van den Hout PhD[2] | Antonis C. Antoniou PhD[3] | Mitul Shah MSc[4] | Lorenzo Ficorella PhD[3] | Emily Steggall MBBS, FFPH[5] | Douglas F. Easton PhD[3] | Paul D. P. Pharoah MBBS, PhD, FRCP[3,6] | Nora Pashayan MD, PhD, FFPH[1]

[1]Department of Applied Health Research, University College London, London, UK

[2]Department of Statistical Science, University College London, London, UK

[3]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

[4]Department of Oncology, University of Cambridge, Cambridge, UK

[5]School of Medicine, Cardiff University, Cardiff, UK

[6]Department of Computational Biomedicine, Cedars Sinai Medical Center, Los Angeles, California, USA

Correspondence

Rikesh Bhatt, Institute Of Health Informatics, University College London, London, UK.
Email: rikesh.bhatt@ucl.ac.uk

Nora Pashayan, Department of Applied Health Research, University College London, London, UK.
Email: n.pashayan@ucl.ac.uk

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Abstract

Background: Genetic, lifestyle, reproductive, and anthropometric factors are associated with the risk of developing breast cancer. However, it is not yet known whether polygenic risk score (PRS) and absolute risk based on a combination of risk factors are associated with the risk of progression of breast cancer. This study aims to estimate the distribution of sojourn time (pre-clinical screen-detectable period) and mammographic sensitivity by absolute breast cancer risk derived from polygenic profile and the other risk factors.

Methods: The authors used data from a population-based case-control study. Six categories of 10-year absolute risk based on different combinations of risk factors were derived using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm. Women were classified into low, medium, and high-risk groups. The authors constructed a continuous-time multistate model. To calculate the sojourn time, they simulated the trajectories of subjects through the disease states.

Results: There was little difference in sojourn time with a large overlap in the 95% confidence interval (CI) between the risk groups across the six risk categories and PRS studied. However, the age of entry into the screen-detectable state varied by risk category, with the mean age of entry of 53.4 years (95% CI, 52.2–54.1) and 57.0 years (95% CI, 55.1–57.7) in the high-risk and low-risk women, respectively.

Conclusion: In risk-stratified breast screening, the age at the start of screening, but not necessarily the frequency of screening, should be tailored to a woman's risk level. The optimal risk-stratified screening strategy that would improve the benefit-to-harm balance and the cost-effectiveness of the screening programs needs to be studied.

KEYWORDS
absolute risk, breast cancer, multistate model, natural history, polygenic risk score, sensitivity, sojourn time

INTRODUCTION

The risk of developing breast cancer varies among women. Breast screening program typically use age as the sole criterion for eligibility. In the United Kingdom, women in the general population 50–69 years old are invited for mammographic screening every 3 years. Screening for breast cancer reduces deaths from the cancer with trade-offs of false findings, overdiagnosis, and overtreatment.[1] Overdiagnosis is the screen-detection of tumors that would not have surfaced clinically in an individual's lifetime in the absence of screening. These trade-offs lead to unnecessary procedures, can create psychological stress, and burden on health care resources.

The majority of women who undergo screening will not develop breast cancer, with one in seven women in the United Kingdom developing cancer in their lifetime.[2] Around one in five of breast cancer diagnoses are in women younger than age 50[3] and around one in 10 of all cancer diagnoses are fast growing cancers that were not detectable at screening but manifested clinically in the interval between two screens.[4] Subsequently, there is a growing call for shifting from one-size-fits-all to a more risk-stratified screening approach.

A risk-stratified screening approach entails assessing the risk of each woman in the population based on a range of risk factors (e.g., genetic, lifestyle, hormonal, and reproductive), stratification of the population risk into several risk groups, and tailoring screening recommendations to each risk group.[5] This approach might mean that some women start mammographic screening at a younger age, have different screening intervals, or have supplemental screening with another imaging modality, such as MRI.[5] To date, several studies have shown that tailoring screening to women's risk level could improve the efficiency of the breast screening program and reduce its adverse consequences.[6–9] There are ongoing studies to determine the barriers and facilitators and the optimal approaches for implementing risk-stratified screening programs.[10] Nevertheless, it is not known how breast cancer risk interacts with the natural history of the cancer to impact the outcomes of screening.

Natural history can be described by the sojourn time, that is, the duration of the period in which a tumor is asymptomatic but detectable by screening. Sojourn time reflects the rate of disease progression: the faster a tumor grows, the shorter the sojourn time. It informs the optimal interval between screens, the likely effectiveness of screening in reducing cancer death, and the extent of overdiagnosis.[11] In particular, screening would need to be offered more frequently to detect fast-growing tumors in the preclinical screen-detectable period. Tailoring screening frequency to the mean sojourn time would optimize the benefit-harm trade-off of screening.

Any natural history model must take into account test sensitivity, i.e., the probability that the screening test will correctly identify an individual with preclinical cancer. The aim of this study was to estimate the sojourn time distribution and mammogram sensitivity by risk levels based on polygenic risk score alone and combined with other risk factors using panel data from the National Health Service Breast Screening Programme (NHSBSP).

MATERIALS AND METHODS

Data

Records of women enrolled in the Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH), a population-based incident case-control study, were linked to the NHSBSP records. SEARCH cases were women younger than age 70 diagnosed between 1989–2019 with invasive breast cancer in East Anglia (N = 15,484) and followed up to 2020. Participants were identified through the Eastern Cancer Registration and Information Centre and were invited through their general practitioner to participate in the study. SEARCH controls (N = 1922) were frequency-matched to cases by age and geographic region. They were free of cancer at the time of recruitment, between 2003–2005. Women who consented to participate completed a questionnaire about breast cancer risk factors and provided a blood sample for genetic profiling. Information on cancer characteristics and cause of death, if applicable, were available only for SEARCH cases.

NHSBSP provided the dates and outcomes of attendance of each screening invitation (screen-detected, interval cancer, cancer in lapsed attender, cancer in non-attender) over the period from 1987 to 2020.

The analysis was based on 9304 women (8309 from SEARCH cases and 995 from SEARCH controls) invited to screening between ages 47 and 70. Observations after an initial detection or diagnosis were removed for women with multiple primary or recurrent breast cancers.

The age-specific mortality rates from other causes among women with and without breast cancer in England from 2016 to 2019 were from the Office for National Statistics (ONS).[12]

Risk scores

The 10-year absolute risk of breast cancer assessed at ages 40 and 50 was estimated for each SEARCH participant using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA),[13] based on six combinations of risk factors. These include age, polygenic risk score based on 313 single-nucleotide polymorphisms (PRS_{313}) explaining 20% of the breast cancer polygenic variance,[14] rare pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *CHECK2*, and *ATM*, family history of breast cancer, and questionnaire-based risk factors (body mass index, alcohol intake, parity, age at first birth, age at menarche, and age at menopause, use of oral contraceptive, and hormone replacement therapy).[13]

The risk-factor combinations for estimating the 10-year absolute risk were age combined with:

RF1: Questionnaire-based risk factors;
RF2: $PRS_{313;}$
RF3: PRS_{313} + family history of breast cancer;
RF4: PRS_{313} + family history of breast cancer + rare pathogenic variants;
RF5: PRS_{313} + family history of breast cancer + questionnaire-based risk factors; and
RF6: PRS_{313} + family history of breast cancer + rare pathogenic variants + questionnaire-based risk factors.

In addition to the 10-year absolute risks, we studied PRS_{313} alone.

For each risk-factor combination and for PRS_{313}, the risk thresholds were based on the relative risk (RR) of breast cancer relative to the population average. SEARCH participants were stratified into three risk groups: "low" ($RR \leq 0.5$), "medium" ($0.5 < RR \leq 2$), and "high" ($RR > 2$) risk. For the risk-factor combination based on questionnaire-based risk factors, there were no participants in either the cases or control group with a relative risk greater than 2. Thus, RF1 participants were stratified as below ($RR \leq 1$) or above the population average risk ($RR > 1$).

MULTISTATE MODEL

We used a nonhomogeneous multistate survival model with age-varying transition hazards between the states of the model and age-varying misclassification.[15] The states of the model are healthy (S1), screen-detectable (S2), clinically diagnosed cancer (S3), and all-cause death (S4). Both S3 and S4 are exact-time absorbing states. We model the progression from healthy to a screen-detectable state to being clinically diagnosed.

The two remaining transitions are transitions to death as a competing risk from S1 and S2. The transitions from S2 to S3 are not directly observed. However, it is possible to estimate the transition from S2 and S3 from subjects who have been screen-detected or clinically diagnosed.[15] The model accounts for data that is left-truncated, interval-censored, and right censored. The transition from S1 to S2 is interval-censored, because the exact transition time is unknown.

The four-state model allows for the possibility of misclassification of S2. A subject in S2 may have had a negative screen test. The probability of misclassification is one minus sensitivity. Here, sensitivity refers to the sensitivity of the screening episode (screening test and subsequent diagnostic procedures).[16]

In estimating the transition hazard between S2 and S3, we reduced the four-state to a three-state model (Figure 1), because the SEARCH cases were recruited after having a cancer diagnosis. The intensity matrix $Q(t)$, at age $t > 0$, is given by

$$Q(t) = \begin{pmatrix} -q_{12}(t) & q_{12}(t) & 0 \\ 0 & -q_{23}(t) & q_{23}(t) \\ 0 & 0 & 0 \end{pmatrix}, \quad (1)$$

where $q_{ij}(t)$ are hazard functions. The transition rates, $q_{ij}(t)$ are given by the Weibull hazard,

$$q_{ij}(t) = \exp(\lambda_{ij} + \tau_{ij}) t^{\exp(\tau_{ij})-1}. \quad (2)$$

The age was rescaled $t \to (t - 19)/10$. We chose this rescaling to prevent numerical overflow. The rescaled age at age 20 is $t = 0.1$ because we require $t > 0$ and the left-truncation age was 20 years old.

The misclassification matrix is

$$E = \begin{pmatrix} 1 & 0 & 0 \\ e_{21} & 1-e_{21} & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad (3)$$

where

$$e_{21} = \Pr(O = 1 | S = 2) = \frac{\exp(\lambda_m)}{1 + \exp(\lambda_m)}, \quad (4)$$

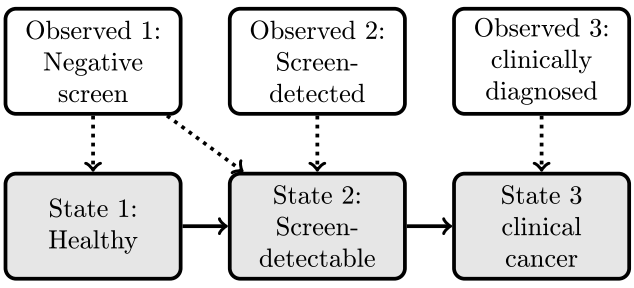

FIGURE 1 Three-state progressive disease. The white boxes are observed states, and the gray boxes are the true underlying state. The solid lines are the transition between true states. Observing a negative screen could be that the person does not have cancer and is in state "healthy" or has screen-detectable cancer but is misclassified. Observations of clinically diagnosed cancers cannot be misclassified in the model.

and a subject is in observed state i when O = i and in true state j when S = j. Misclassification is 0%, 50%, and 100% when the misclassification parameter is $\lambda_m = -\infty$, $\lambda_m = 0$, and $\lambda_m = \infty$.

The parameter estimates were derived by maximizing the likelihood function using the Nelder-Mead algorithm.[15] We stratified the data by risk groups and fit a model separately for each risk group.

Sojourn time

Sojourn time is the time length from screen-detectable time to clinical diagnosis time. To calculate the sojourn time, we developed a micro-simulation algorithm in Box 1 using the natural history parameters and national statistics on death rates by age. We simulated the trajectories of 10,000 women from age 20 through the three states. In the algorithm, we implement death from all causes (S4) as competing risk to account for death between screen-detectable state (S2) and clinical diagnosis (S3). Any individual that dies before S3 would not contribute to the calculation of sojourn time. We calculated the length of time in the preclinical screen-detectable state, S2, for those who have entered into S3.

BOX 1 Natural history simulation algorithm.

1. Simulate the death age of a subject, T
2. Simulate the age of entry into State 2, t_2. Using the parameters we derive

$$t_2 = \exp\left(\frac{\log\left(-U\exp(\lambda_{12}) + t_1\exp(\tau_{12})\right)}{\exp(\tau_{12})}\right)$$

where U ~ [0, 1]. Also, $t_1 = 0.1$ is the transformed left truncation age corresponding to 20 years old.

3. **If** $T > t_2$ **then**
   a. Keep t_2
   Simulate the age of entry into State 3, t_3 where

$$t_3 = \exp\left(\frac{\log\left(-U\exp(\lambda_{23}) + t_1\exp(\tau_{23})\right)}{\exp(\tau_{23})}\right)$$

   b. **If** $T > t_3$ **then**
   Keep t_3 and remove T
   Else
   Keep T and remove t_3
   End if

Else
Keep T and remove t_2
End if

There are two orders of uncertainty in calculating the mean sojourn time. The uncertainty arises from the randomness of simulating the trajectories and from the parameter estimation.[17] To account for the uncertainty related to stochastic processes, we simulated a large number of trajectories. For the uncertainty in the parameter estimation, we used 200 parameter sets derived from the parameter estimates and the covariance matrix. The calculation of the 95% confidence interval (CI) for the mean sojourn time is determined from the 200 simulations.

Model validation

We simulated the trajectories of 50,000 women through the states using the algorithm in Box 1, then we imposed a screening strategy with 3-yearly screening from ages 47 to 70, as in the NHSBSP. We compared the proportion of cancer diagnoses as interval cancers in the simulated cohort versus the observed in the SEARCH study.

RESULTS

Cancer characteristics and detection mode

On average, SEARCH participants attended 3.1 screening rounds (range, 0–9), with 5.1% never attending a screening and 66% attending all screening invitations. The median age at the first screen was 51 years.

Of the 8309 cancers, 97.8% were invasive, 1.8% in situ, and 0.4% cancers had unspecified stage information. Of the cancers with known hormone status, 85.1% (5280 of 6208) were estrogen receptor-positive (ER+), 66.6% (1783 of 2677) were progesterone receptor-positive (PR+), and 11.4% (406 of 3573) were human epidermal growth factor receptor 2-positive (HER2+). Of cancers where hormone status was known for all three receptors, 13.1% (279 of 2134) were triple-negative (Table 1).

Overall, 58% (N = 4832) of the breast cancers were screen-detected. A total of 65.9% (N = 3186), 22.4% (N = 1081), 3.9% (N = 190) and 1.9% recorded ER+, PR+, HER2+, and triple-negative, respectively (Table 1). A larger proportion of interval cancers were ER-negative (ER–), PR-negative (PR–), and HER2+. Of the 3477 clinically diagnosed cancers, 13.6% were among never attenders, 14.4% among lapsed attenders, and 72% were interval cancers.

Among the interval cancers, 18.4% were diagnosed within the first year, 38.3% within the second year, and 43.3% between the second and third year. The distribution of the timing of interval cancers by hormone specific subtypes is presented in Table SA1 in the Supporting Information.

Risk distribution

Table 2 shows the proportion of women in the three risk groups for each of the risk-factor combinations.

The mean (SD) absolute risk scores for women with cancer were 3.9 (2.6), 2.2 (0.5), 3.4 (1.6), 3.6 (1,9), 4.2 (4.6), 3.1 (1.8), and 3.5 (4.1)

TABLE 1 Breast cancer subtypes in SEARCH by age at diagnosis and detection modality.

	Total	Screen detected	Mean (SD) age at screen detection, years	Clinically diagnosed (interval cancers)	Mean (SD) age at clinical diagnosis, years
Breast cancers	8309	4832	59.0 (5.7)	3477 (2478)	59.8 (5.4)
Subtypes					
Invasive	8101	4670	59.1 (5.7)	3431 (2449)	59.8 (5.4)
In situ	148	114	56.2 (4.7)	32 (24)	60.0 (5.5)
Unknown	26	15	60.1 (6.7)	11 (6)	59.5 (5.3)
ER status					
Positive	5280	3186	59.1 (5.8)	2094 (1501)	60.1 (5.8)
Negative	928	380	58.6 (5.2)	548 (410)	59.3 (5.3)
PR status					
Positive	1783	1081	58.6 (5.8)	702 (499)	59.6 (5.4)
Negative	894	409	59.6 (5.3)	485 (353)	59.4 (5.4)
HER2 status					
Positive	406	190	59.0 (4.9)	216 (165)	59.3 (5.2)
Negative	3167	1185	59.4 (5.8)	1282 (940)	60.0 (5.4)
ER–, PR–, and HER2–					
Triple-negative	279	94	58.5 (5.4)	185 (138)	58.9 (5.3)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SEARCH, Studies of Epidemiology and Risk Factors in Cancer Heredity.

for PRS alone and risk factors RF1 to RF6, respectively. The mean (SD) absolute risk scores for women absent of cancer were 2.7 (1.9), 2.4 (0.4), 2.6 (1.4), 2.6 (1.4), 2.7 (2.3), 2.2 (1.2), and 2.4 (2.2) for PRS alone and risk factors RF1 to RF6, respectively. There is little difference in the risk scores of women that have been screen-detected versus women that have clinically diagnosed tumors. The largest disparity was in RF3 (PRS313 + family history of breast cancer) which was 0.4, and there was a mean difference of 0.1 in all the risk factors.

Dependent on the combination of risk factors, 15%–26% of women without breast cancer diagnosis would be in the low-risk group and 3%–5% in the high-risk group. In contrast, among women with breast cancer, only 4%–13% would be categorized as low-risk and 9%–15% as high-risk. Compared to RF2, adding family history and rare pathogenic variants identified a larger proportion of women with breast cancer at high risk, whereas adding questionnaire-based risk factors identified a larger proportion of women at lower risk. Compared to RF2, adding family history and rare pathogenic variants identified a larger proportion of women with breast cancer at high risk, whereas adding questionnaire-based risk factors identified a larger proportion of women at lower risk.

The percentage of screen-detected cancers in the low-risk groups ranged from 5% to 12% except for RF1, which accounted for 83% of the screen-detected cancers. A range of 78%–84% of the screen-detected cancers were from the medium-risk groups. The percentage of screen-detected cancers from the high-risk groups ranged from 9% to 16% (17% for the high-risk group of RF1). The percentage of interval-diagnosed cancers that were in the low-risk groups ranged from 4% to 13% except for RF1, which accounted for 86% of the interval cancers. A range of 72%–84% of the interval cancers were from the medium-risk groups. The percentage of interval-diagnosed cancers from the high-risk groups ranged from 9% to 20% (14% for the high-risk group of RF1). The percentage of other clinically diagnosed cancers (in lapsed or non-attenders) that were in the low-risk groups ranged from 5% to 13% except for RF1, which accounted for 86% of the non-interval clinically diagnosed cancers. A range of 74%–82% of the other clinically diagnosed cancers were from the medium-risk groups. The percentage of other clinically diagnosed cancer from the high-risk groups ranged from 10% to 19% (14% for the high-risk group of RF1).

Natural history of breast cancer

Sojourn time estimates

Tables SA2 and SA3 show the estimated natural history parameters. Overall, the mean sojourn time was estimated to be 3.1 years (95% CI, 2.8–3.3 years), and the median sojourn time was 2.2 years (interquartile range [IQR], 1.9–2.4 years). Breast cancer subtypes ER–, PR–, and HER2+ had shorter sojourn time than ER+, HER2–, and PR+ subtypes, respectively (Table 3). Furthermore, the sojourn

TABLE 2 The mean age (SD) at screen detection and clinical diagnosis and the % of women at low, average, and high risk for each of the six risk-factor combinations and healthy state.

	Women without breast cancer (%)	Screen detected (%)	Clinically diagnosed (%)	Mean age (SD) at screen detection, years	Mean age (SD) at clinically diagnosis, years
PRS: PRS_{313} alone					
Low	23	8	8	59.1 (5.5)	60.4 (5.5)
Medium	70	72	72	59.1 (5.7)	59.9 (5.3)
High	8	20	20	58.7 (5.7)	59.4 (5.5)
RF1: age + questionnaire-based risk factors					
Low	79	83	86	59.1 (5.8)	60.0 (5.4)
High	21	17	14	58.4 (5.3)	59.0 (5.1)
RF2: age + PRS_{313}					
Low	15	4	4	59.4 (5.6)	60.1 (5.7)
Medium	80	84	84	59.1 (5.7)	59.9 (5.3)
High	5	12	12	58.5 (5.7)	59.3 (5.7)
RF3: age + PRS_{313} + family history of breast cancer					
Low	15	5	4	59.5 (5.4)	60.4 (5.6)
Medium	80	81	81	59.1 (5.7)	59.9 (5.4)
High	5	15	15	58.4 (5.7)	59.2 (5.5)
RF4: age + PRS_{313} + family history of breast cancer + rare pathogenic variants					
Low	16	5	5	59.3 (5.5)	60.6 (5.6)
Medium	79	79	78	58.4 (5.7)	59.9 (5.4)
High	5	16	17	58.4 (5.7)	59.3 (5.5)
RF5: age + PRS_{313} + family history of breast cancer + questionnaire-based risk factors					
Low	25	11	13	59.6 (5.6)	60.7 (5.4)
Medium	73	80	78	59.0 (5.8)	59.8 (5.4)
High	3	9	9	58.4 (5.6)	59.0 (5.3)
RF6: age + PRS_{313} + family history of breast cancer + rare pathogenic variants + questionnaire-based risk factors					
Low	26%	12%	13%	59.5 (5.7)	60.8 (5.4)
Medium	70%	78%	75%	59.0 (5.7)	59.8 (5.4)
High	4%	11%	11%	58.1 (5.5)	59.0 (5.3)

Note: Low refers to a relative risk of less than 1 for RF1 and ≤0.5 for the other risk-factor combinations. Medium refers to a relative risk of >0.5 and ≤2. High refers to a relative risk of ≥1 for RF1 and >2 for the other risk-factor combinations.

time of triple-negative cancers was shorter than the other breast cancer subtypes. The mean sojourn time, estimated from parameters in Table SA5, for DCIS cancers was 4.9 years (95% CI, 1.6–6.3 years) with a median of 3.5 years (IQR, 1.1–4.6 years).

Figure 2 shows the distribution of sojourn time by risk level for the six risk-factor combinations. The mean sojourn time among the risk groups was comparable across the risk-factor combinations (Table 3).

The sojourn time by risk level, PRS, and risk factor RF6 and hormone subtypes (ER+, ER−, PR+, and PR−) is presented in Table SA4 in the Supporting Information. The mean sojourn time of ER+, stratified by risk level, ranged from 2.9 to 3.6 years and ER− ranged from 1.5 to 2.1 years. The mean sojourn time of PR+, stratified by risk level, ranged from 2.8 to 3.7 years and PR− ranged from 1.6 to 2.5 years.

Age of entry into preclinical screen-detectable state

The mean age of onset of preclinical screen-detectable cancer, determined from the parameter estimates in Table SA2, was 54.5 years (95% uncertainty range, 54.4–55.1 years). The age of entry into the screen-detectable state varied by risk strata, with a lower mean age for the high-risk group compared to the low-risk group. In the risk factor combination based on PRS and family

TABLE 3 Sojourn time, age of entry to preclinical state, and misclassification by hormone status and by risk level for each of the risk combinations.

		Misclassification (95% CI)	Sojourn time (years)		Age of entry into State 2
			Mean (95% CI)	Median (95% CI)	Mean (95% CI)
ER	Neg	14.3 (8.7–22.0)	1.7 (1.4–2.0)	1.2 (1.0–1.4)	55.7 (52.8–57.0)
ER	Pos	4.7 (3.2–6.6)	2.9 (2.8–3.3)	2.1 (1.9–2.4)	55.5 (55.1–55.9)
HER2	Neg	12.3 (8.6–16.8)	3.3 (1.4–3.6)	2.3 (0.9–2.6)	56.7 (55.7–57.5)
HER2	Pos	0.5 (0.0–37.1)	1.9 (0.1–2.0)	1.2 (0.0–1.3)	59.8 (53.9–62.1)
PR	Neg	13.0 (6.4–22.2)	2.1 (0.6–2.3)	1.5 (0.3–1.6)	59.2 (56.2–60.4)
PR	Pos	11.7 (7.7–16.7)	3.2 (1.2–3.6)	2.2 (0.7–2.6)	56.1 (53.6–57.1)
Triple	Neg	8.7 (2.3–27.5)	1.3 (0.6–1.6)	0.9 (0.4–1.1)	52.2 (48.1–53.7)
PRS	Low	5.4 (2.3–13.8)	2.9 (2.2–3.2)	2.1 (1.6–2.4)	57.4 (55.8–58.2)
PRS	Medium	12.2 (10.2–14.7)	3.1 (2.9–3.3)	2.1 (2.0–2.4)	54.5 (53.9–54.8)
PRS	High	10.2 (6.4–14.8)	3.2 (2.8–3.5)	2.2 (1.9–2.5)	53.5 (52.5–54)
RF1	Low	9.1 (7.5–11.1)	2.9 (2.8–3.2)	2.0 (1.9–2.3)	55.3 (54.7–55.6)
RF1	High	10.8 (6.5–16.9)	3.6 (2.4–4.1)	2.4 (1.7–2.9)	54.4 (53.3–55)
RF2	Low	0.7 (0–12.1)	2.8 (1.0–3.1)	1.9 (0.7–2.2)	56.8 (51.5–58.1)
RF2	Medium	11.1 (8.9–13.4)	3.1 (2.9–3.3)	2.1 (2.0–2.4)	54.9 (54.3–55.1)
RF2	High	10.1 (6–17.6)	3.4 (2.5–3.6)	2.4 (1.7–2.6)	53.4 (52.2–54.2)
RF3	Low	7.4 (2.6–17)	3.0 (2.2–3.6)	2.0 (1.6–2.5)	58.0 (56.1–58.8)
RF3	Medium	9.9 (8.1–12.1)	3.1 (2.8–3.4)	2.2 (1.9–2.4)	55.4 (54.8–55.6)
RF3	High	10.3 (5.6–15.9)	3.2 (2.6–3.5)	2.3 (1.8–2.5)	53.0 (52.1–53.8)
RF4	Low	0.5 (0–12)	2.9 (2.0–3.3)	2.0 (1.4–2.3)	57.9 (56–58.7)
RF4	Medium	10.4 (8.4–12.9)	3.2 (2.9–3.4)	2.3 (1.9–2.4)	55.0 (54.5–55.3)
RF4	High	10.1 (6.3–15.2)	3.1 (2.5–3.3)	2.1 (1.7–2.4)	53.4 (52.2–54)
RF5	Low	9.7 (5.9–14.8)	2.8 (2.2–3.0)	1.9 (1.5–2.1)	57.0 (55.7–57.5)
RF5	Medium	9.7 (8–11.9)	3.3 (2.9–3.4)	2.2 (2.0–2.4)	54.7 (54.2–55)
RF5	High	10.2 (4.5–17.8)	3.3 (2.4–3.8)	2.3 (1.6–2.7)	53.2 (51.6–54)
RF6	Low	9.4 (5.6–15.3)	2.7 (2.4–3.0)	2.0 (1.6–2.2)	56.7 (55.8–57.4)
RF6	Medium	0.4 (0.1–1.3)	2.7 (2.5–3.0)	1.8 (1.7–2.1)	54.2 (53.6–54.6)
RF6	High	9.9 (5.5–16.6)	3.0 (2.2–3.3)	2.2 (1.5–2.3)	53.0 (51.6–53.7)

Abbreviations: CI, confidence interval; Neg, negative; Pos, positive; RF1, age + questionnaire–based risk factors; RF2, age + PRS313; RF3, RF2 + FH; RF4, RF3 + rare pathogenic variants; RF5, RF1 + RF3; RF6, RF1 + RF5.

history (RF3), there was 5 years difference between the high- and low-risk groups (mean age of 53 vs. 58 years, respectively) (Table 3).

Table SA6 shows the mean age of onset of preclinical screen-detectable cancer when risk is assessed at age 40. The estimates were similar to those with risk assessed at 50.

Misclassification

The overall misclassification was estimated as 9.7% (95% CI, 8.3%–11.8%), giving an episode sensitivity of 90.3% (95% CI, 88.2%–91.7%). ER+ breast cancers had higher episode sensitivity (95.3%; 95% CI, 93.4%–96.8%) than ER− cancers (85.7%; 95% CI, 78.0%–91.3%). However, there was little difference in episode sensitivity among the risk groups and across the risk-factor combinations (Table 3).

Model validation

In the simulated cohort, with 100% screening attendance, 34.9% of all cancer diagnoses were estimated to be interval cancers. In SEARCH, 31.6% (N = 2237) of all cancer diagnoses among regular attenders of breast screening were interval cancers, suggesting that the model fit was good.

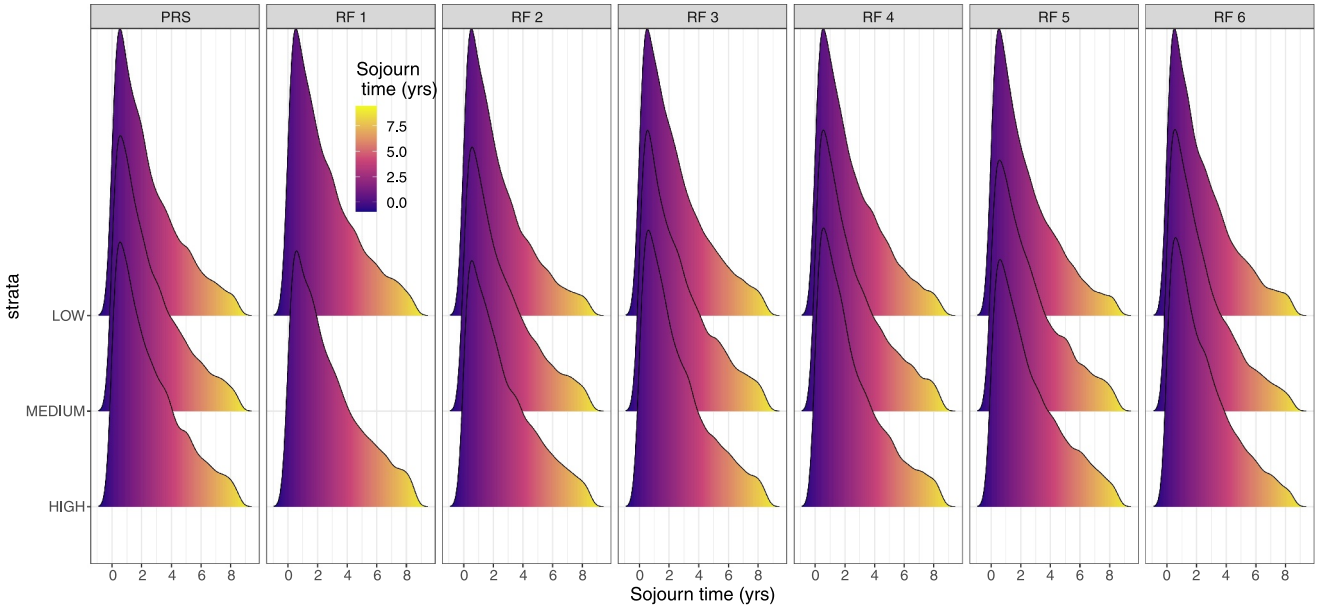

FIGURE 2 Sojourn time distribution by polygenic risk score (PRS_{313}) and 10-year absolute risk combinations and risk strata. RF1: age + questionnaire based risk factors; RF2: age + PRS_{313}; RF3: RF2 + FH; RF4: RF3 + rare pathogenic variants; RF5: RF1 + RF3; RF6: RF1 + RF5.

DISCUSSION

To our knowledge, this is the first study to report on the natural history of breast cancer for different risk groups. We used individualized risk predictions based on PRS alone and six combinations of risk factors: age, questionnaire-based risk factors, family history, PRS, and rare pathogenic variants. For each woman in the SEARCH study, we calculated her PRS and 10-year absolute risk of breast cancer, assessed at different ages, using the BODICEA algorithm. We linked the data to each woman's NHSBSP records of screening attendance and outcome for every screening invitation from age 47 to 70 or age at censoring over the period from 1987 to 2020. We chose to employ stratification instead of incorporating the risk score into the multistate model. This decision allows us to separately analyze data within each risk stratum, potentially yielding more meaningful and unbiased insights into the natural progression of breast cancer. This approach mitigates the risk of circular reasoning or potential confounding that might arise from directly including risk scores as variables in the model. We found that the sojourn time distribution and the episode sensitivity were relatively similar among the risk groups. However, the age of entry into the screen-detectable state varied by risk group. Women in the high-risk group had screen-detectable cancer on average at an earlier age than those in the low-risk group.

Sojourn time is not directly observable. In a systematic review of 33 published studies, Geurts et al.[18] identified several different mathematical approaches (maximum likelihood estimation, Bayesian Markov Chain Monte Carlo simulation, regression of observed on expected, and expectation-maximization algorithm) used to estimate sojourn time.

When the different approaches were applied to the same data source, different estimates were obtained.[18] The reported estimates of the mean sojourn time of breast cancer range from 2 to 7 years and sensitivity from 59% to 90%.[18,19] Our estimate of mean sojourn time of 3.1 years is comparable to previous estimates derived with Markov multistate modeling for women 50–69 years old.[20–23] This sojourn time in the context of screening every 3 years explains the high proportion of cancers being diagnosed as interval cancers. Our findings of shorter sojourn time for ER–, PR–, and HER2+ cancer subtypes are consistent with the more aggressive behavior of these subtypes. The estimated mean sojourn time for DCIS was longer than for invasive cancers, but the CI is large.

There are no previous estimates of sojourn time by risk level in which to compare our results. However, the finding that sojourn time does not vary substantially by risk group, that is, higher risk is not associated with faster progression or more aggressive disease, is aligned with other studies. Taghipour et al.[23] used multistate models to investigate the effect of several breast cancer risk factors (other types of breast disease, family history of breast cancer, years from menarche to menopause, and number of live births) on the state transition rates and misclassification probability. None of these risk factors affected the estimates of sojourn time and episode sensitivity. Isheden et al.[24] found no association between the rate of lymph node spread, a measure of tumor aggressiveness, and PRS. Cardozo et al.[25] and Li et al.[26] found that interval cancers were associated with lower PRS. Our results show agreement with Ishden et al.[24] and Cardozo et al.[25] because our results show little difference in the sojourn time between low risk and high risk based on PRS. Lower-risk cancers had shorter sojourn time than higher-risk cancers, although this difference was not significant.

Earlier onset of breast cancer in women with a higher risk must be considered in the design of a risk-stratification program. However, risk-stratification must overcome many hurdles before its adoption

as part of a screening program. The way risk-stratification is implemented remains open, particularly regarding organizational issues.[10] The cost-effectiveness or benefit-harm ratio of risk-stratified screening must also be assessed.[27]

Although the more aggressive cancer subtypes are often more common in younger women,[28] we found no significant difference in the age of onset of screen-detectable hormone status positive and negative cancers. This could be because of missing hormone status data. Only 26.4% of SEARCH cases had information on ER, PR, and HER2 status. Because the analysis was limited to women invited to screening from age 47, the natural history of the more aggressive cancers clinically diagnosed at a younger age was not feasible to study.

Limitations

In SEARCH, by study design, women with cancer vastly outnumber women without cancer. Therefore, the estimates of the transition rate from State 1 to State 2 reflect that for women with breast cancer diagnosis rather than for the population at large. However, this does not affect the transition from State 2 to State 3 (i.e., sojourn time estimates). The participants of the SEARCH study were from East of England and predominantly of European ancestry. The generalizability of the findings to women from different ancestral backgrounds, particularly of African descent, remains uncertain.

Our multistate model is a progressive disease model that assumes that all screen-detectable cancers will become symptomatic after a finite time, in the absence of competing risks such as screen detection and death. This assumption could underestimate the sojourn time.

There is the potential for survival bias as the participation in SEARCH is based on women's survival until the enrollment time. The sojourn time would be overestimated in the presence of survival bias.

Strengths

We have used individual-level data with information on risk factors linked to the national cancer registry and national screening program. Our model allows for left truncated data, where the true state at the first observation is unknown because of misclassification or not having had screening.

In conclusion, estimates of sojourn time within the context of risk guide the development of tailored screening strategies that are aimed at improving the likelihood of early detection of cancer before it progresses to symptomatic state. The absolute risk of breast cancer, dependent on age and PRS alone or combined with other risk factors, is associated with the early onset of preclinical screen-detectable breast cancer. However, it is not associated with the risk of progression from preclinical screen-detectable to symptomatic clinical cancer. In risk-stratified breast screening, the age of start of screening but not necessarily the frequency of screening would be tailored to a woman's risk level. Further studies are needed to identify the optimal risk-stratified screening strategies that could improve the benefit-to-harm, and the cost-effectiveness, ensure the acceptability, and promote equitable access to risk-stratified breast screening program.

AUTHOR CONTRIBUTIONS

Rikesh Bhatt: Writing–original draft, writing–review and editing, formal analysis, methodology, and conceptualization. **Ardo van den Hout**: Writing–review and editing, conceptualization, and methodology. **Antonis C. Antoniou**: Data curation and writing–review and editing. **Mitul Shah**: Writing–review and editing and data curation. **Lorenzo Ficorella**: Writing–review and editing and data curation. **Emily Steggall**: Writing–review and editing and data curation. **Douglas F. Easton**: Writing–review and editing and data curation. **Paul D. P. Pharoah**: Writing–review and editing and data curation. **Nora Pashayan**: Conceptualization, methodology, formal analysis, writing–review and editing, and writing–original draft.

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CONFLICT OF INTEREST STATEMENT

BOADICEA has been licensed by Cambridge Enterprise and Antonis C. Antoniou is listed as a creator. Douglas F. Easton received payments to their institution for the licensing of the BOADICEA/CanRisk risk prediction algorithm. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request. Requests for SEARCH data should be made to the SEARCH Team (SEARCH.Info@medschl.cam.ac.uk).

ORCID

Rikesh Bhatt https://orcid.org/0000-0003-3924-3619

Nora Pashayan https://orcid.org/0000-0003-0843-2468

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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