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Article

Cumulative Advanced Breast Cancer Risk Prediction Model Developed in a Screening Mammography Population

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Abstract

Background: Estimating advanced breast cancer risk in women undergoing annual or biennial mammography could identify women who may benefit from less or more intensive screening. We developed an actionable model to predict cumulative 6-year advanced cancer (prognostic pathologic stage II or higher) risk according to screening interval. **Methods:** We included 931 186 women aged 40-74 years in the Breast Cancer Surveillance Consortium undergoing 2 542 382 annual (prior mammogram within 11-18 months) or 752 049 biennial (prior within 19-30 months) screening mammograms. The prediction model includes age, race and ethnicity, body mass index, breast density, family history of breast cancer, and prior breast biopsy subdivided by menopausal status and screening interval. We used fivefold cross-validation to internally validate model performance. We defined higher than 95th percentile as high risk (>0.658%), higher than 75th percentile to 95th or less percentile as intermediate risk (0.380%-0.658%), and 75th or less percentile as low to average risk (<0.380%). **Results:** Obesity, high breast density, and proliferative disease with atypia were strongly associated with advanced cancer. The model is well calibrated and has an area under the receiver operating characteristics curve of 0.682 (95% confidence interval = 0.670 to 0.694). Based on women's predicted advanced cancer risk under annual and biennial screening, 69.1% had low or average risk regardless of screening interval, 12.4% intermediate risk with biennial screening and average risk with annual screening, and 17.4% intermediate or high risk regardless of screening interval. **Conclusion:** Most women have low or average advanced cancer risk and can undergo biennial screening. Intermediate-risk women may consider annual screening, and high-risk women may consider supplemental imaging in addition to annual screening.

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Most US women who undergo screening mammography have annual screenings (1-4) despite calls for reduced screening intensity and tailored decision making to improve the screening effectiveness of healthy women (5,6). Screening mammography randomized controlled trials showed a 20% reduction in breast cancer mortality among women aged 50-74 years whether screened annually or biennially, with annual screening resulting in almost twofold more false-positive mammograms and benign biopsies (7-10). Modeling studies show incremental reductions in breast cancer deaths averted with annual vs biennial screening in average-risk women (10) and greater reductions in annually screened women at high risk (11,12).

Screening mammography results in decreased breast cancer mortality by reducing advanced breast cancer incidence (8,13,14). Advanced breast cancer [American Joint Committee on Cancer (15) anatomic stage IIB or higher or prognostic

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pathologic stage II or higher] occurs in 22%-24% of routinely screened women diagnosed with invasive breast cancer (16-18) and results in worse survival than early stage disease (17-19). We previously showed the combination of high breast density and high 5-year breast cancer risk could identify women with elevated advanced cancer risk, though with limited sensitivity (17). Defining combinations of risk factors that categorize women at high risk of developing advanced cancer despite screening could identify those who may benefit from more effective screening strategies.

We developed the first actionable model to predict cumulative 6-year advanced breast cancer risk (2,17,20,21) so we could compare cumulative risk for women undergoing 6 annual vs 3 biennial screens according to breast cancer risk factors commonly collected in clinical practice. Our goal is to inform clinical decisions about screening frequency and supplemental imaging for individuals at low or average, intermediate, or high advanced breast cancer risk undergoing routine screening.

Methods

Study Setting and Data Sources

Data were from the Breast Cancer Surveillance Consortium (BCSC) mammography registries (https://www.bcsc-research.org/), whose population demographics are comparable to the US population (22-24). We prospectively collected data on women's characteristics and mammography information from radiology facilities. Breast cancer diagnoses and tumor characteristics were obtained by linking women to pathology databases; regional Surveillance, Epidemiology, and End Results programs; and state tumor registries. Deaths were obtained by linking to state death records. Registries and a central statistical coordinating center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analyses. All procedures were Health Insurance Portability and Accountability Act compliant, and registries and the statistical coordinating center received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

Participants

Screening mammograms were defined based on radiologist's report of clinical indication. To reflect women routinely screened, we identified 3 507 682 screening mammograms performed from January 2005 through December 2017 among women aged 40-74 years with a mammogram 11-30 months earlier representing more than 94% of subsequent screens (25). Annual screening was defined as having a prior mammogram within 11-18 (mean = 13.8) months and followed for 12 months to determine occurrence of breast cancer or death. Biennial screening was defined as having a prior mammogram within 19-30 (mean = 23.7) months and followed for 24 months for outcomes. See Supplementary Table 1 (available online) and Figure 1 for distributions by screening intervals. We excluded screens from women with a breast cancer history (n = 174 028), mastectomy (n = 11 094), or lobular carcinoma in situ (n = 1917) because a more intensive screening strategy is recommended for these women. We also excluded screening mammography that was unilateral, preceded by mammography within 9 months (n = 19 483), performed with a screening ultrasound on the same day (n = 726), or screening magnetic resonance imaging (MRI) that occurred 12 months before or after (n = 6003), leaving 3 294 431 annual or biennial screens (25% film, 69% digital, 5% tomosynthesis, 1% unspecified).

Measures, Definitions, and Outcomes

We collected demographic and breast health history from self-administered surveys at each screening and/or extracted from electronic health records. Radiologists categorized breast density during clinical interpretation using breast imaging reporting and data system (26) density categories: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense. Postmenopausal women were those with both ovaries removed, periods had stopped naturally, current postmenopausal hormone therapy use, or aged 60 years or older. Premenopausal women reported a period within the last 180 days or birth control hormone use. Perimenopausal women were not sure if their periods had stopped or their last menstrual period was 180-364 days prior (27-29). Body mass index (BMI) was categorized as less than 18.5 kg/m^2 underweight, 18.5-24.9 kg/m^2 normal weight, 25.0-29.9 kg/m^2 overweight, 30.0-34.9 kg/m^2 obese I, and 35.0 kg/m^2 or more obese II or III (30).

Breast biopsy results were abstracted from clinical pathology reports. We grouped prior benign diagnoses based on the highest grade as proliferative with atypia higher than proliferative without atypia higher than nonproliferative using published taxonomy (31-34) or as unknown if a woman reported a prior biopsy with no available BCSC pathology result.

Mammograms were linked to invasive breast cancer or ductal carcinoma in situ diagnoses within 12 months after annual and 24 months after biennial mammography. We calculated American Joint Committee on Cancer, 8th edition, prognostic, pathologic stage (15) using anatomic staging elements; tumor grade; and estrogen, progesterone, and human epidermal growth factor receptor status. We defined advanced cancer as prognostic stage II or higher because it has better accuracy for predicting 5-year breast cancer mortality than anatomic stage (18). If prognostic stage could not be calculated (15%), we used anatomic stage IIb or higher (12%) or other information (3%).

Statistical Approach

Analyses were performed using the screening mammogram as the unit of analysis unless otherwise specified. We characterized mammograms associated with no advanced cancer or advanced cancer for annual and biennial screens according to risk factors. We estimated absolute advanced cancer risk, irrespective of mode of detection, and competing events (death or early stage cancer) within 12 months after an annual screen or 24 months after a biennial screen using logistic regression. Separate models were fit by menopausal status (premenopausal vs perimenopausal and postmenopausal) and screening interval and included age (linear and quadratic), race and ethnicity, first-degree breast cancer family history, history of benign biopsy, BMI, and breast density. Before model fitting, 15 imputed values for each missing variable were generated using multiple imputation chained equations (35). For each covariate combination, risk scores from a single screening round were estimated by averaging over the 15 risk scores estimated from each imputed dataset. Model calibration was estimated by the ratio of expected to observed advanced cancers for predicted risk decile groups. Model discriminatory accuracy was summarized using the area under the receiver operating characteristic curve (AUC)

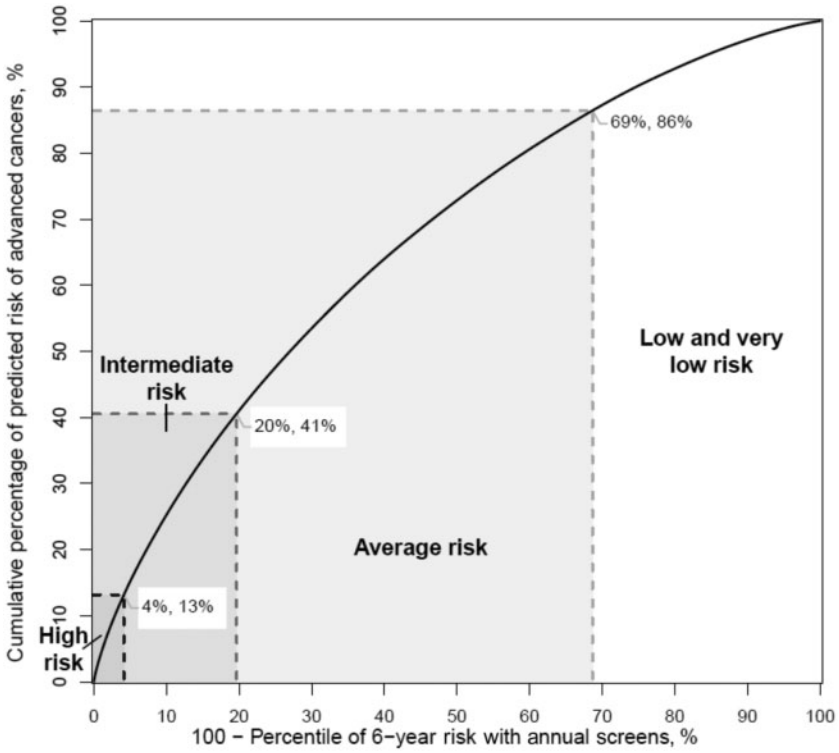

Figure 1. Cumulative percentage of predicted risk of advanced cancers (stage II or higher) among annual screeners stratified by cumulative percentage of 6-year advanced cancer risk sorted from highest to lowest risk. The shaded regions indicate 4 risk groups: high risk, >95th percentile; intermediate risk, >75th and ≤95th percentile; average, >25th and ≤75th percentile; low and very low risk, ≤25th percentile.

to compare predicted risk after 1 screening round based on a woman's observed screening interval and risk factors to the observed outcome of advanced cancer within 1 year of an annual screen or 2 years of a biennial screen. To internally validate the model, we compared the AUC from the model fit using the full data to the AUC from the model fit using fivefold cross-validation, and the difference between them (optimism) was 0.013. To account for the small overfitting, the adjusted AUC and 95% confidence intervals (CI) were calculated after subtracting the optimism from the estimates obtained from full data.

The cumulative advanced cancer risks after 6 annual and 3 biennial screens were estimated using a discrete time survival model based on the fitted logistic regression models for each screening round while considering competing risks of death or early stage cancer within 1 year after annual or 2 years after biennial screening (36). Advanced cancer could occur after any annual or biennial screen during the 6-year follow-up period. Mean 6-year cumulative risks and interquartile ranges for annual and biennial screening were standardized to the US population of women based on age, race and ethnicity, and breast cancer family history by weighting the overall study population (37,38). According to 6-year cumulative advanced cancer risk, women were categorized into 5 risk levels (high, >95th percentile; intermediate, >75th to ≤95th percentile; average, >25th and ≤75th percentile; low, >5th and ≤25th percentile; very low, ≤5th percentile) and combined into 3 risk levels for calculation of prevalence of risk groups by screening interval (>95th percentile as high risk [>0.658%], >75th to <95th percentile as intermediate risk [0.380%-0.658%], and <75th percentile as low to average risk [<0.380%]). The Supplementary Methods and Supplementary Table 2 (available online) provide additional statistical methods details.

Data were analyzed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC). Two-sided alpha of 0.05 was used to determine statistical significance.

Results

The study cohort included 931 186 women aged 40-74 years undergoing 2 542 382 annual and 752 049 biennial screening mammograms who developed 1110 and 760 advanced cancers and 7297 and 4237 nonadvanced cancers, respectively. Compared with women screened biennially, women screened annually tended to be older and have a breast cancer family history and history of breast biopsy (Table 1).

In multivariable-adjusted models, obesity, dense breasts (heterogeneously or extremely dense), and proliferative disease with atypia were strongly associated with advanced cancer (Table 2). The associations of breast cancer family history and dense breasts with advanced cancer were stronger for premenopausal than postmenopausal women, and the associations of overweight or obesity and Black, non-Hispanic race with advanced cancer were stronger for postmenopausal women. Associations with advanced cancer for postmenopausal, obese I biennial screeners were stronger than for annual screeners, whereas obese II and III annual screeners had higher advanced cancer risk. The strength of benign breast disease associations with advanced cancer did not vary by screening interval or menopausal status.

Overall, biennial screeners had 1.5-fold higher proportion of women at intermediate or high advanced cancer risk compared with annual screeners (Table 3). Women aged 40-59 years had the highest proportion in the very low and low advanced cancer

Table 1. Characteristics of women undergoing annual and biennial screening

Characteristics	Annual (n = 2 542 382)					Biennial (n = 752 049)				
	No advanced cancer[a]		Advanced breast cancer[b]			No advanced cancer[a]		Advanced breast cancer[b]		
	No.	Column, %	No.	Column, %	Row, %	No.	Column, %	No.	Column, %	Row, %
Screening examinations[c]	2 541 267	99.96	1110	—[d]	0.04	751 285	99.90	760	—[d]	0.10
Age, y										
40-49	633 753	24.9	198	17.8	0.03	206 148	27.4	159	20.9	0.08
50-59	895 381	35.2	396	35.7	0.04	280 198	37.3	272	35.8	0.10
60-69	759 869	29.9	389	35.0	0.05	206 723	27.5	251	33.0	0.12
70-74	252 264	9.9	127	11.4	0.05	58 216	7.7	78	10.3	0.13
Race and ethnicity										
Asian/Pacific Islander	237 823	9.4	72	6.5	0.03	102 763	13.7	88	11.6	0.09
Black, non-Hispanic	228 253	9.0	192	17.3	0.08	66 261	8.8	103	13.6	0.16
Hispanic	116 719	4.6	48	4.3	0.04	47 418	6.3	40	5.3	0.08
White, non-Hispanic	1 797 793	70.7	736	66.3	0.04	487 396	64.9	493	64.9	0.10
Other/mixed	42 626	1.7	22	2.0	0.05	18 856	2.5	19	2.5	0.10
Unknown	118 053	4.6	40	3.6	0.03	28 591	3.8	17	2.2	0.06
Menopausal										
No	632 688	24.9	237	21.4	0.04	203 065	27.0	184	24.2	0.09
Yes	1 454 112	57.2	708	63.8	0.05	416 189	55.4	463	60.9	0.11
Unknown	454 467	17.9	165	14.9	0.04	132 031	17.6	113	14.9	0.09
First-degree family history of breast cancer[e]										
No	2 000 401	78.7	802	72.3	0.04	632 629	84.2	614	80.8	0.10
Yes	443 781	17.5	270	24.3	0.06	96 810	12.9	127	16.7	0.13
Unknown	97 085	3.8	38	3.4	0.04	21 846	2.9	19	2.5	0.09
History of breast biopsy										
None (no prior biopsy)	1 948 017	76.7	717	64.6	0.04	627 322	83.5	565	74.3	0.09
Prior biopsy, benign diagnosis unknown	388 553	15.3	262	23.6	0.07	90 950	12.1	153	20.1	0.17
Nonproliferative	142 949	5.6	91	8.2	0.06	24 025	3.2	30	3.9	0.12
Proliferative without atypia	52 226	2.1	31	2.8	0.06	7974	1.1	10	1.3	0.13
Proliferative with atypia	9522	0.4	9	0.8	0.09	1014	0.1	2	0.3	0.20
BI-RADS breast density										
Almost entirely fat	236 336	9.3	40	3.6	0.02	71 988	9.6	25	3.3	0.03
Scattered fibroglandular densities	1 069 779	42.1	360	32.4	0.03	296 890	39.5	235	30.9	0.08
Heterogeneously dense	981 763	38.6	512	46.1	0.05	292 213	38.9	312	41.1	0.11
Extremely dense	207 731	8.2	109	9.8	0.05	62 774	8.4	74	9.7	0.12
Unknown	45 658	1.8	89	8.0	0.19	27 420	3.6	114	15.0	0.41
Body mass index, kg/m^2										
Underweight (<18.5)	25 654	1.0	10	0.9	0.04	8190	1.1	5	0.7	0.06
Normal (18.5-24.9)	700 038	27.5	231	20.8	0.03	216 024	28.8	177	23.3	0.08
Overweight (25.0-29.9)	480 818	18.9	190	17.1	0.04	150 198	20.0	173	22.8	0.12
Obese I (30.0-34.9)	252 175	9.9	102	9.2	0.04	81 359	10.8	103	13.6	0.13
Obese II/III (≥35.0)	182 208	7.2	103	9.3	0.06	65 515	8.7	53	7.0	0.08
Unknown	900 374	35.4	474	42.7	0.05	229 999	30.6	249	32.8	0.11

[a]Includes nonadvanced breast cancers. AJCC = American Joint Committee on Cancer; BI-RADS = Breast Imaging Reporting and Data System.
[b]Invasive cancer AJCC 8th edition prognostic pathologic stage II or higher within 12 or 24 months of screening mammography.
[c]Subsequent screening examinations.
[d]Not applicable.
[e]Defined as first-degree relative (mother, sister, or daughter) with breast cancer.

risk groups, whereas women aged 60-74 years had the highest proportion in the intermediate and high-risk groups.

The AUC for predicting advanced cancer was 0.682 (95% CI = 0.670 to 0.694). Supplementary Figures 2 and 3 (available online) show the overall ratios of expected to observed advanced cancers for annual and biennial screeners are 1.0.

Among annual screeners, the 19.7% identified as intermediate or high risk is expected to have 40.6% of advanced cancers (Figure 1), and the 31.3% identified as very low or low risk is expected to have 13.5% of advanced cancers. Among the biennial screeners, the 30.3% identified as intermediate or high risk is expected to have 51.2% of advanced cancers, and the 19.0% identified as very low or low risk is expected to have 7.2% of advanced cancers (Figure 2).

Based on women's predicted advanced cancer risk under annual and biennial screening, 69.1% had low or average advanced cancer risk whether undergoing annual or biennial screening, 12.4% intermediate risk with biennial screening and average

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Table 2. Multivariable odds ratios for advanced breast cancer by breast cancer risk factors and screening interval and menopausal status

	Advanced prognostic stage II or higher[a]			
	Annual		Biennial	
Risk factors	Premenopausal OR (95% CI)	Postmenopausal OR (95% CI)	Premenopausal OR (95% CI)	Postmenopausal OR (95% CI)
Age, y—linear term	0.98 (0.91 to 1.06)	1.03 (1.00 to 1.05)	1.01 (0.93 to 1.11)	1.05 (1.02 to 1.08)
Age, y—quadratic term	0.99 (0.99 to 1.00)	1.00 (1.00 to 1.00)	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.00)
Race and ethnicity				
Asian//Pacific Islander	0.79 (0.51 to 1.24)	0.82 (0.60 to 1.10)	0.66 (0.41 to 1.09)	1.03 (0.79 to 1.35)
Black, non-Hispanic	1.65 (1.16 to 2.36)	1.94 (1.61 to 2.35)	1.17 (0.75 to 1.82)	1.53 (1.17 to 1.99)
Hispanic	0.75 (0.41 to 1.39)	1.33 (0.95 to 1.87)	0.98 (0.59 to 1.63)	0.84 (0.55 to 1.28)
White, non-Hispanic	Referent	Referent	Referent	Referent
Other/Mixed	1.39 (0.65 to 2.97)	1.28 (0.76 to 2.14)	0.87 (0.36 to 2.11)	1.11 (0.65 to 1.91)
First-degree family history of breast cancer[b]				
Yes	1.61 (1.21 to 2.13)	1.37 (1.16 to 1.60)	1.44 (1.00 to 2.07)	1.20 (0.95 to 1.51)
No	Referent	Referent	Referent	Referent
History of breast biopsy				
No prior biopsy	Referent	Referent	Referent	Referent
Prior biopsy, benign diagnosis unknown	1.73 (1.25 to 2.40)	1.58 (1.34 to 1.87)	1.79 (1.23 to 2.61)	1.60 (1.29 to 1.97)
Nonproliferative	1.36 (0.85 to 2.17)	1.64 (1.27 to 2.11)	1.30 (0.66 to 2.54)	1.24 (0.79 to 1.95)
Proliferative without atypia	1.08 (0.48 to 2.43)	1.65 (1.10 to 2.47)	1.34 (0.43 to 4.19)	1.24 (0.57 to 2.67)
Proliferative with atypia	2.43 (0.60 to 9.82)	2.18 (1.03 to 4.60)	0.00 (0.00 to Inf)	2.37 (0.59 to 9.52)
BI-RADS breast density				
Almost entirely fat	0.41 (0.15 to 1.14)	0.44 (0.31 to 0.62)	0.40 (0.13 to 1.25)	0.38 (0.24 to 0.59)
Scattered fibroglandular densities	Referent	Referent	Referent	Referent
Heterogeneously dense	2.29 (1.64 to 3.20)	1.82 (1.55 to 2.13)	1.85 (1.27 to 2.69)	1.61 (1.32 to 1.97)
Extremely dense	2.64 (1.71 to 4.06)	2.41 (1.78 to 3.25)	2.44 (1.49 to 3.99)	2.11 (1.45 to 3.06)
Body mass index, kg/m^2				
Underweight (<18.5)	0.64 (0.19 to 2.10)	1.32 (0.74 to 2.36)	0.79 (0.25 to 2.49)	1.20 (0.61 to 2.38)
Normal (18.5-24.9)	Referent	Referent	Referent	Referent
Overweight (25.0-29.9)	1.31 (0.93 to 1.85)	1.42 (1.14 to 1.76)	1.72 (1.19 to 2.49)	1.61 (1.22 to 2.11)
Obese, grade I (30.0-34.9)	1.38 (0.88 to 2.18)	1.72 (1.35 to 2.20)	1.54 (0.97 to 2.42)	2.07 (1.58 to 2.71)
Obese, grade II/III (≥35.0)	1.83 (1.17 to 2.86)	2.30 (1.80 to 2.95)	1.40 (0.79 to 2.48)	1.85 (1.30 to 2.65)

[a]Invasive cancer AJCC 8th edition prognostic pathologic stage II or higher within 12 or 24 months of screening mammography; models adjusted for age and its quadratic term, race and ethnicity, first-degree breast cancer family history, history of benign biopsy, body mass index, and breast density. AJCC = American Joint Committee on Cancer; BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; OR = odds ratio.
[b]Defined as first-degree relative (mother, sister, or daughter) with breast cancer.

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risk with annual screening, and 17.4% intermediate or high risk regardless of screening interval (data not shown). For example, postmenopausal obese I women on average had an intermediate advanced cancer risk of 0.454% when biennially screened but an average risk of 0.341% when annually screened (Figure 3), suggesting postmenopausal obese I women may benefit from annual screening. In contrast, advanced cancer risk was intermediate regardless of whether annual or biennial screening for postmenopausal women with heterogeneously dense breasts (mean = 0.395% and 0.451%, respectively), extremely dense breasts (mean = 0.452% and 0.501%, respectively), or a breast cancer family history (mean = 0.391% and 0.425%, respectively). Postmenopausal women with proliferative disease with atypia had the highest advanced cancer risk whether annually or biennially screened (mean = 0.596% and 0.790%, respectively) suggesting this group may benefit from supplemental imaging in addition to annual screening.

Among women at intermediate risk with biennial screening and average risk with annual screening, 12.7% had prognostic pathologic stage II or higher under annual screening vs 15.9% under biennial screening (Supplementary Table 3, available online). Women at intermediate or high advanced cancer risk with annual and biennial screening had a similar proportion of advanced stage regardless of screening interval.

Supplementary Tables 4 and 5 (available online) show the combinations of age, breast density, and BMI that result in high, intermediate, average, or low 6-year cumulative risk for biennial and annual screeners. For example, obese I women aged 60-74 years with scattered fibroglandular densities are at intermediate advanced breast cancer risk with biennial screening and could reduce their 6-year cumulative advanced cancer risk to average risk levels with annual screening, whereas women aged 40-69 years with heterogeneously dense breasts and normal BMI are at average advanced cancer risk whether they

Table 3. Prevalence of cumulative risk of advanced cancer after 6 years of annual or biennial screening for high, intermediate, average, low, and very low risk groups[a]

	Annual					Biennial				
Measure	Very low (<0.089%)	Low (0.090-0.171%)	Average (0.172-0.379%)	Intermediate (0.380-0.658%)	High (>0.658%)	Very low (<0.089%)	Low (0.090-0.171%)	Average (0.172-0.379%)	Intermediate (0.380-0.658%)	High (>0.658%)
Overall risk, mean %	0.068	0.132	0.255	0.480	0.865	0.069	0.136	0.269	0.485	0.846
Overall percentage of women	6.9	24.5	49.0	15.5	4.1	3.1	15.9	50.6	24.5	5.9
Percentage of women within age group										
40-49	12.8	33.4	42.9	9.3	1.7	5.7	23.6	53.8	15.0	2.0
50-59	5.0	24.7	50.1	16.2	4.0	2.4	15.8	50.9	25.2	5.7
60-69	3.6	17.3	53.1	20.0	6.0	1.6	9.7	47.0	32.3	9.4
70-74	4.3	17.1	52.4	19.5	6.6	2.1	10.6	50.5	28.6	8.2

[a]Risk threshold based on distribution of risk in combined sample of annual and biennial screeners; high risk; >95th percentile, intermediate risk; >75th and ≤95th percentile, average risk; >25th and ≤75th percentile, low risk; >5th and ≤25th percentile, very low risk; ≤5th percentile. Risk and prevalence adjusted by US population weights and standardized to same population for annual and biennial.

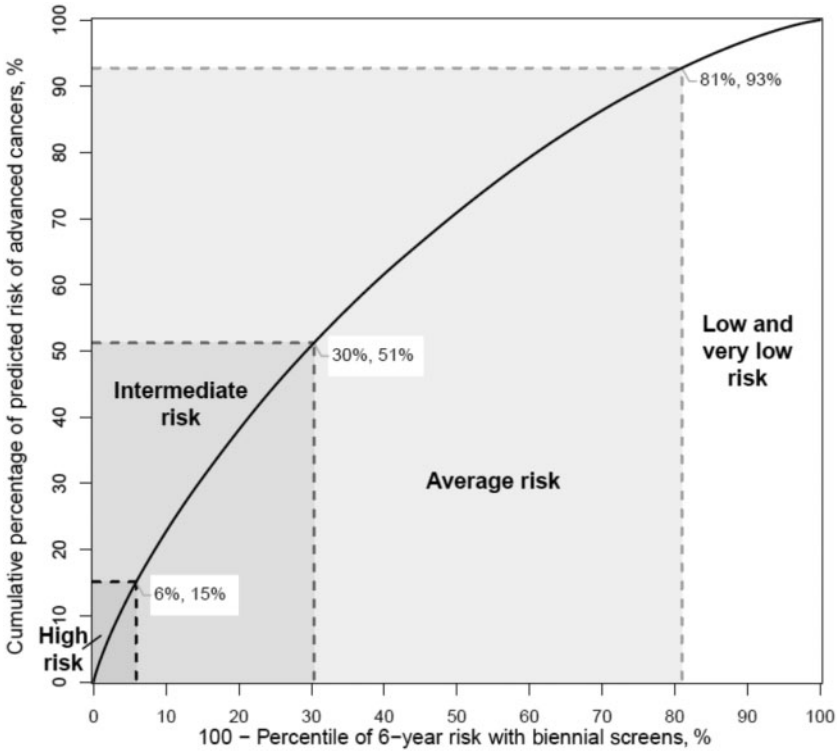

Figure 2. Cumulative percentage of predicted risk of advanced cancers (stage II or higher) among biennial screeners stratified by cumulative percentage of 6-year advanced cancer risk sorted from highest to lowest risk. The shaded regions indicate 4 risk groups: high risk, >95th percentile; intermediate risk, >75th and ≤95th percentile; average, >25th and ≤75th percentile; low and very low risk; ≤25th percentile.

undergo annual or biennial screening. Overweight or obese women aged 40-49 years can consider mammography to determine if they have dense breasts and are at high or intermediate advanced cancer risk.

Discussion

Risk-based screening individualizes screening recommendations for women based on their level of breast cancer risk with a goal of improving early detection of aggressive breast cancers before they present as advanced breast cancer, while minimizing screening harms. We found age, race and ethnicity, breast density, BMI, breast cancer family history, history of benign biopsy, and menopausal status can be used to identify women at high advanced breast cancer risk to inform clinical decisions about screening frequency and possibly supplemental imaging. Most women (69%) were at low to average advanced breast cancer risk regardless of screening interval suggesting these women can undergo biennial screening to avoid the more frequent harms associated with annual screening (2,39). In

	Premenopausal			Postmenopausal		
	Mean cumulative 6−yr risk of Advanced Cancer %		Risk difference from biennial to annual	Mean cumulative 6−yr risk of Advanced Cancer %		Risk difference from biennial to annual
	Biennial screener	Annual screener	Mean (IQR) %	Biennial screener	Annual screener	Mean (IQR) %
Overall	0.287	0.227		0.351	0.296	
Body mass index, kg/m^2						
Underweight (<18.5)	0.214	0.145		0.376	0.354	
Normal (18.5–24.9)	0.240	0.202		0.268	0.230	
Overweight (25.0–29.9)	0.372	0.240		0.381[b]	0.296[b]	
Obese I (30.0–34.9)	0.307	0.240		0.454[b]	0.341[b]	
Obese II/III (>=35.0)	0.246	0.280		0.361	0.409	
Age, y						
40 – 49	0.265	0.215		0.201	0.239	
50 – 59	0.366	0.271		0.316	0.280	
60 – 69	–	–		0.389[b]	0.311[b]	
70 – 74	–	–		0.365	0.309	
Benign breast disease						
No prior biopsy	0.256	0.203		0.304	0.252	
Prior biopsy, diagnosis unknown	0.521[a]	0.397[a]		0.528[a]	0.431[a]	
Non–proliferative	0.368	0.309		0.407[a]	0.440[a]	
Proliferative without atypia	0.371	0.233		0.404[a]	0.437[a]	
Proliferative with atypia	–	0.581		0.790[a]	0.596[a]	
BI–RADS breast density						
Almost entirely fat	0.085	0.066		0.131	0.126	
Scattered fibroglandular densities	0.203	0.142		0.320	0.253	
Heterogeneously dense	0.339	0.286		0.451[a]	0.395[a]	
Extremely dense	0.383[b]	0.286[b]		0.501[a]	0.452[a]	
1st degree family history of breast cancer						
No	0.273	0.213		0.339	0.281	
Yes	0.431[b]	0.374[b]		0.425[a]	0.391[a]	
Race/ethnicity						
Asian/pacific Islander	0.184	0.168		0.312	0.193	
Black, non–Hispanic	0.352	0.382		0.555[a]	0.549[a]	
Hispanic	0.279	0.158		0.262	0.314	
White, non–Hispanic	0.288	0.217		0.334	0.260	
Other/mixed	0.247	0.299		0.361	0.321	

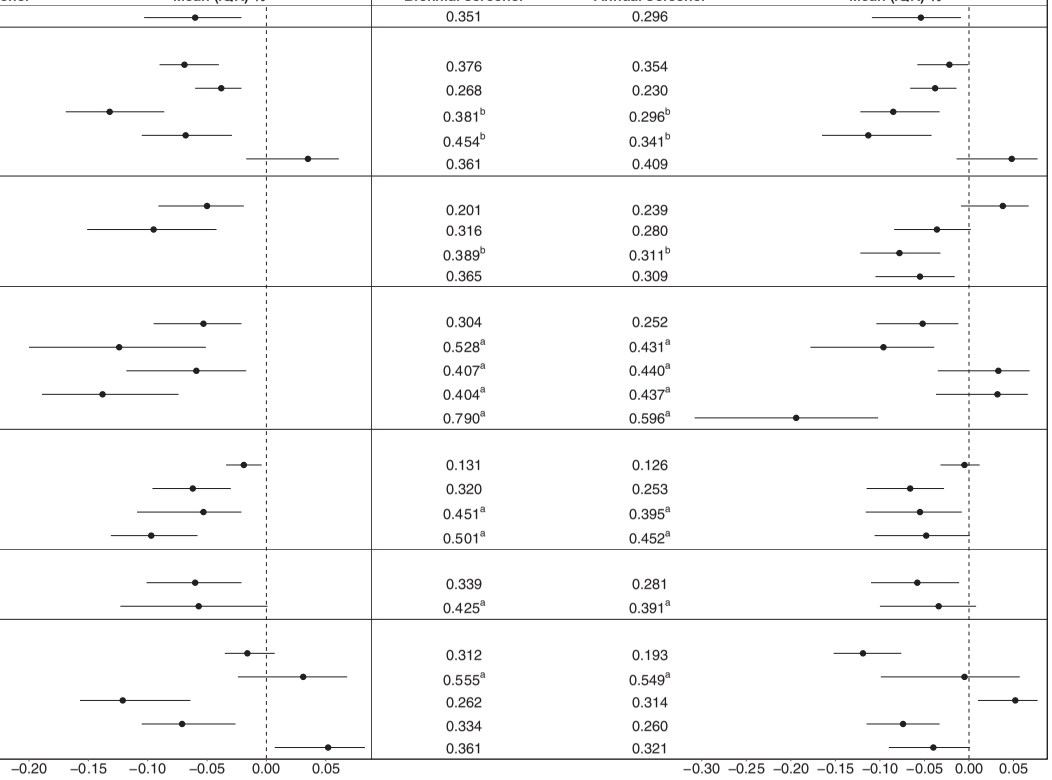

Figure 3. Mean cumulative risk of advanced breast cancer (stage II or higher) after 6 years of annual vs biennial screening and mean absolute risk difference from biennial to annual screening. Absolute risk difference not shown for proliferative disease with atypia because differences are so large estimates are off the graph. Estimates are based on a model including age, breast cancer family history, breast density, breast biopsy, body mass index, and race and ethnicity. Adjusted by US population weights and standardized to same population for annual and biennial. [a]Intermediate or high risk with biennial and annual screening. [b]Intermediate risk with biennial screening and average risk with annual screening. — = Absolute risk difference not applicable for ages 60-74 for premenopausal women; BI-RADS = Breast Imaging Reporting and Data System; IQR = interquartile range.

contrast, we found 12% of women were at intermediate advanced breast cancer risk with biennial screening and average risk with annual screening, suggesting they might benefit from receiving annual screening. We also found 17% of women had intermediate or high risk regardless of screening interval and may consider supplemental imaging in combination with annual screening; however, future studies need to evaluate whether supplemental imaging reduces advanced cancer incidence.

Risk prediction is an essential component of risk-based screening. Available models predict invasive breast cancer risk overall (34,40), which is not uniformly correlated with advanced breast cancer risk among racial and ethnic groups (41). Characterizing women at high advanced cancer risk in the screening setting facilitates identifying women who may benefit from a more intensive screening strategy other than biennial screening, which may enable earlier detection of aggressive tumors that could reduce breast cancer mortality and/or lead to less aggressive treatment (8,13,42). The breast cancer preclinical phase is estimated to be 10 years, but breast cancer only may be detectable with mammography 3 to 8 years before symptom onset (43,44), suggesting an effective advanced cancer risk model used for individualizing screening should predict at least 5-year risk to allow for sufficient time to detect breast cancer at an early stage. Allowing for sufficient time to implement risk assessment and effective screening strategies is supported by the observation that it takes 3 to 4 years of screening before a decrease in incidence of advanced breast cancer is observed (45). Plus, short-term risk is more applicable to screening decisions and likely more accurate for risk stratification (46,47). Thus, we calculated 6-year cumulative advanced breast cancer risk such that women biennially screened would undergo 3 screening rounds and women annually screened would undergo 6 screening rounds. Our advanced cancer risk model is well calibrated and the AUC comparable to overall breast cancer risk prediction models (Gail, Tyrer-Cuzick, BCSC) in use in clinical practice to recommend referral for genetic testing and/or primary prevention (48,49).

Increasing age, dense breasts, and obesity have been associated with advanced breast cancer risk (42,50-52) and breast cancer mortality (53). If age was the only criteria used to identify women at increased advanced cancer risk, all postmenopausal women aged 60-69 years would be considered at intermediate to high advanced cancer risk with biennial screening. Likewise, if only breast density or BMI was used to identify women at increased advanced cancer risk, all postmenopausal women with dense breasts or those overweight or category obese I would be considered at intermediate to high advanced cancer risk with biennial screening. Notably, studies have shown high BMI and breast density have additive effects on breast cancer risk such that women with high BMI and high breast density have very high breast cancer risk (54,55). Our results extend these findings by showing women at highest advanced cancer risk had a combination of risk factors (eg, obese, aged 60 years and older, and dense breasts). We also found having a breast cancer family history, proliferative disease with atypia, and Black race were associated with advanced breast cancer risk. This suggests an actionable risk model that includes a combination of risk factors to predict advanced breast cancer should be used to inform screening frequency and supplemental imaging to optimize early detection of aggressive breast cancers before they present as advanced cancer and minimize the harms of frequent screening among low and average advanced cancer risk women.

Two randomized controlled trials have reported a 50% reduction in interval breast cancer rate with mammography plus supplemental imaging compared with mammography alone (10,56,57). In the intention to treat analysis, the Dense Tissue and Early Breast Neoplasm Screening randomized controlled trial showed no difference in the proportion of women with lymph node–positive disease in the supplemental MRI plus mammography vs mammography alone groups after the first screening round (57). In a MRI-screened cohort of mutation carriers (58), annual MRI surveillance was associated with a statistically significant reduction in the incidence of advanced-stage breast cancer compared with undergoing mammography alone. These studies suggest supplemental imaging may reduce screening failures.

We studied a large, diverse, population-based sample of women undergoing annual or biennial screening, which makes our results most applicable to regular screeners. We modeled the probability of an advanced cancer within 12 months of an annual screening mammogram and 24 months of a biennial screening mammogram with most annual screening occurring within 11-14 months and biennial within 19-26 months, a reflection of community practice. Biennial and annual screeners had different distributions of characteristics included in the risk models, and US population weights were used to standardize to the same population. However, residual confounding still could impact risk estimates. Some estimated confidence intervals are wide because of small sample sizes resulting in variability of risk estimates. We did not assess outcomes associated with supplemental screening for women with high advanced cancer risk. Our study does not address optimal advanced cancer risk thresholds or individual preferences for advanced cancer risk thresholds. Harms were not assessed, but published studies have reported the cumulative risk of false-positive mammography and biopsy by screening interval and reported almost twofold greater harms with annual vs biennial screening (2,59). Although we internally validated our model using cross-validation, our model needs to be externally validated.

Reducing advanced breast cancer incidence decreases breast cancer mortality and morbidity from cancer treatment. This is the first actionable risk model to predict advanced breast cancer among women with a recent screening mammogram where risk is linked to a screening interval. We report groups of women at intermediate or high advanced breast cancer risk with biennial screening, who may consider annual screening, and women at high advanced cancer risk despite annual screening, who may consider supplemental imaging. We also identified women at low or average advanced breast cancer risk who can undergo biennial screening to reduce their chance of false-positive recall and benign biopsy. We are developing an online risk calculator that can be used in clinical practice prior to requesting routine screening to determine a woman's advanced breast cancer risk with annual or biennial screening to inform screening decisions.

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Notes

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Data Availability

The data underlying this article will be shared on reasonable request and approval by the BCSC Steering Committee (https://www.bcsc-research.org/).

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