Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

Research Article

Cancer Prevention Research

Assessing the Breast Cancer Risk Distribution for Women Undergoing Screening in British Columbia

Christina R. Weisstock[1], Rasika Rajapakshe[1], Christabelle Bitgood[2], Steven McAvoy[1], Paula B. Gordon[3], Andrew J. Coldman[4], Brent A. Parker[1], and Christine Wilson[5]

Abstract

Breast cancer risk estimations are both informative and useful at the population level, with many screening programs relying on these assessments to allocate resources such as breast MRI. This cross-sectional multicenter study attempts to quantify the breast cancer risk distribution for women between the ages of 40 to 79 years undergoing screening mammography in British Columbia (BC), Canada. The proportion of women at high breast cancer risk was estimated by surveying women enrolled in the Screening Mammography Program of British Columbia (SMPBC) for known breast cancer risk factors. Each respondent's 10-year risk was computed with both the Tyrer–Cuzick and Gail risk assessment models. The resulting risk distributions were evaluated using the guidelines from the National Institute for Health and Care Excellence (United Kingdom). Of the 4,266 women surveyed, 3.5% of women between the ages of 40 to 79 years were found to have a high 10-year risk of developing breast cancer using the Tyrer–Cuzick model (1.1% using the Gail model). When extrapolated to the screening population, it was estimated that 19,414 women in the SMPBC are considered to be at high breast cancer risk. These women may benefit from additional MRI screening; preliminary analysis suggests that 4 to 5 additional MRI machines would be required to screen these high-risk women. However, the use of different models and guidelines will modify the number of women qualifying for additional screening interventions, thus impacting the MRI resources required. The results of this project can now be used to inform decision-making groups about resource allocation for breast cancer screening in BC. *Cancer Prev Res; 6(10); 1084–92. ©2013 AACR.*

Introduction

The Screening Mammography Program of British Columbia (SMPBC) currently provides regular mammograms for eligible women between the ages of 40 to 79 years (1). For the past several years, the screening policy recommended by the SMPBC has been primarily based on age, with women between the ages of 40 to 49 years receiving annual reminder letters, women ages 50 to 79 years sent biennial reminders, and women outside these age groups eligible to receive mammograms upon physician referral (1). However, there are risk factors other than age that significantly raise a woman's risk of developing breast cancer. Recognized risk factors include a family history of breast and ovarian cancer (particularly if the individual harbors a *BRCA1/2* gene mutation), high mammographic breast density, elevated body mass index (BMI), early menarche and late menopause, prolonged nulliparity, previous breast biopsy, abnormal biopsy findings, and the use of hormone replacement therapies (HRT; refs. 2, 3). Therefore, a relatively young woman could have a markedly increased risk of breast cancer but may not be identified as such based on her age alone. This is an issue that will likely need to be addressed by screening programs in the future, as it is now known that these risk factors may substantially influence breast cancer risk independent of age (4).

As the shift toward personalized medicine continues, it is becoming increasingly useful to obtain accurate estimates of breast cancer risk to optimize the prevention and early detection of the disease. Accordingly, a wide variety of models have been developed to compute a woman's risk of developing breast cancer based on personal and familial risk factors. Established risk assessment models include Tyrer–Cuzick (5), Gail (6), Claus (7), Ford (8), BOADICEA (9), and BRCAPRO (10), which have been used to quantify breast cancer risk in various settings. However, these models base their respective risk computations on different aspects of a woman's personal and familial history, and thus are not equally well calibrated for all populations (11). Both the Tyrer–Cuzick and Gail models incorporate a variety of

Authors' Affiliations: [1]BC Cancer Agency, Medical Physics, Kelowna, BC; [2]University of British Columbia, Southern Medical Program, Kelowna, BC; [3]BC Women's Hospital & Health Centre, Sadie Diamond Breast Program, Vancouver, BC; [4]BC Cancer Agency, Population Oncology, Vancouver, BC; and [5]BC Cancer Agency, Diagnostic Imaging, Vancouver, BC

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Rasika Rajapakshe, BC Cancer Agency, Centre for the Southern Interior, 399 Royal Avenue, Kelowna, BC, V1Y 5L3. Phone: 250-712-3915; Fax: 250-979-4018; E-mail: rrajapak@bccancer.bc.ca

doi: 10.1158/1940-6207.CAPR-13-0027

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

hereditary and nonhereditary risk factors (Supplementary Table S1), and have been recently evaluated in their computation of 10-year breast cancer risk (12). The use of risk assessment models to recommend breast MRI screening for high-risk women has been implemented in the United States, United Kingdom, and in Ontario, Nova Scotia, and Alberta, Canada (13–15).

Despite the many benefits and increased cancer detection rate of MRI surveillance, it is neither cost effective nor reasonable to screen all women with this highly sensitive, but expensive modality (16, 17). Perhaps the most important limitation to breast MRI relates to its low specificity, which has been found to range widely from 75% to 98% (compared with a specificity of 91% to 100% for mammography), although the prognostic value becomes more favorable in women with high familial risk and/or a *BRCA1/2* gene mutation (18, 19). The decreased specificity of MRI often leads to additional investigation and work-up, which may include potentially unnecessary biopsies. These procedures can be expensive and anxiety inducing for the woman, and steps should be taken to minimize the occurrence of false-positive screening results (20, 21). One effective way to maximize benefits and reduce harms is to tailor the screening program to provide additional screening for only the women who are at a high risk of developing breast cancer, as these are the women who will attain the greatest benefit from adjunct screening.

Therefore, the objective of this study was to determine the proportion of women in BC's screening program at high risk of developing breast cancer, using the Tyrer–Cuzick risk assessment model. As a comparison, the Gail model was also used to estimate the breast cancer risk of the same population. To our knowledge, this is the first study to directly compare the full risk distributions of the Tyrer–Cuzick and Gail models on a population level. Similar risk assessments have been conducted in other geographic locations (22–25), but findings from previous studies may not be directly applicable to the screening population of BC. It is also important to assess breast cancer risk in the context of BC's provincial health care system; knowing the proportion of women at high risk is a useful aid for decision making and the allocation of health care resources, ultimately allowing the impact of various risk-based surveillance and prevention policies to be estimated.

Materials and Methods

A survey questionnaire was developed to collect the personal information and family cancer history of women attending the SMPBC. Survey questions corresponded to the parameters of the Tyrer–Cuzick model and included age, height, weight, ethnicity, ages of menarche and menopause, parity, HRT use, previous oophorectomy, prior breast biopsies, and any abnormal biopsy findings such as ductal carcinomas *in situ* (DCIS) or lobular carcinomas *in situ* (LCIS). Extensive family history of cancer was also obtained for all first-, second-, and third-degree relatives, including parents, grandparents, aunts and uncles, nieces and nephews, cousins, children, siblings, and half-siblings. Where applicable, the type of cancer and age at diagnosis were both recorded, as well as any available genetic testing information for the respondent and family members.

A sample of women enrolled in the SMPBC was recruited to the study by staff and volunteers; each participating woman gave voluntary consent. The study sample was composed of two cohorts of women. The first cohort included women from three screening mammography centers in BC: Kelowna (Site A), Victoria General Hospital in Victoria (Site B), and BC Women's Health Centre in Vancouver (Site C) between August 2009 and January 2010. Surveys were distributed by on-site volunteers and clerks. Respondents participated in the study in three ways; they could complete the survey by mail, phone, or a website dedicated to this project (26). Phone interviews were held at the woman's convenience, and a database was developed to gather and store respondent information. In addition to this first cohort of women, a second group was later recruited by mailing the same survey out with the woman's regular SMPBC mammogram reminder letter. Mailing out the surveys increased the sample size and allowed for the representation of additional, more remote communities of BC. This second cohort of women returned the questionnaire by mail. All respondents were assigned a unique ID to maintain anonymity and confidentiality.

Each woman's 10-year risk of developing breast cancer was computed using both the Tyrer–Cuzick and Gail models (5, 6). Tyrer–Cuzick risks were computed automatically using the IBIS Risk Evaluator (Version 6.0, released August 2004; ref. 27). After the completion of this study, a newer version of the Tyrer–Cuzick model was released (Version 7.0, June 2013; ref. 27). Risk estimates using the Gail model (Version 3.0, May 2011) were computed by an in-house interface using the publicly available Gail model source code for the calculation engine (28). Since the completion of our work, a special SAS macro, updated December 2012, is now also available to project breast cancer risks using the Gail model in batch mode (29). Given that the Gail model does not include the presence of *BRCA1/2* mutations and is not recommended for women with a history of DCIS and LCIS, Gail risks were calculated assuming that the women were *BRCA*-negative and without a history of LCIS. None of the respondents in the SMPBC had a personal history of DCIS or previous breast cancer. As the cases of *BRCA1/2* and LCIS were relatively few in number (3 *BRCA*-positive women and 2 women with LCIS in the total sample of 4,266), it is not expected that this substantially affected the Gail model estimates. To ensure reproducibility of risk estimates, batch processed 10-year and lifetime risks from the Tyrer–Cuzick IBIS evaluator were compared with the interactive version for 50 randomly selected respondents. Batch calculated 5-year and lifetime risks from the Gail model source code were compared with the online calculator's estimates for 50 randomly selected women. Risk estimates for both models in batch mode were found to agree exactly with the risk outputs of the corresponding risk assessment tools.

From the risk outputs obtained, women were then classified into risk categories using guidelines from the United

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

Kingdom's National Institute for Health and Care Excellence (NICE; London, United Kingdom). High risk is defined by the NICE guidelines as having a risk "more than 8%" of developing breast cancer in the next 10 years (14). Moderate 10-year risk is a 3% to 8% probability of developing breast cancer, and low risk is below 3%, which is approximately equivalent to the risk of the general population. As both the Tyrer–Cuzick and Gail risk assessment models provide 10-year breast cancer risk estimates, the NICE guidelines were used to classify women as high-risk in both models. Using data from BC Stats and the SMPBC, the number of high-risk women eligible for adjunct breast screening in BC was extrapolated from the risk distribution of the study sample. MRI resource calculations were based on the expert opinion of radiologists specializing in breast imaging.

This project was approved by the British Columbia Cancer Agency Research Ethics Board (UBC BCCA REB Certificate #H09-00681).

Results and Discussion

In total, 4,266 women completed the survey, with 3,035 (71%) obtained from the first cohort of women who were recruited "in-clinic" and 1,231 (29%) from the second "mail-out" cohort. Of the three screening clinics, only Site B was able to facilitate the documentation of response rate; study uptake at this site was found to be 47%. This is comparable with the on-site study uptake of 31% to 50% in a similar risk assessment study conducted by Evans and colleagues (23). Despite the low response rate of the "mail-out" respondents (10%), the two cohorts were not statistically different in the majority of their risk factor distributions. χ^2 tests for frequency distributions showed that the two cohorts differed significantly at the 0.05 level for 5 of the 22 risk factors analyzed (age, ethnicity, Ashkenazi inheritance, current/previous HRT use, and second-degree cancer history) but did not statistically differ for the other 17 risk factors (education, previous biopsy, number of biopsies, abnormal biopsy findings, age at menarche, age at menopause, HRT type, intended length of HRT use, oophorectomy, age at oophorectomy, parity, age at first birth, number of births, ovarian cancer history, genetic test results, first-degree cancer history, and cancer history in all relatives). The cohorts had average 10-year Tyrer–Cuzick risks of 3.31% and 3.24% for the "in-clinic" and "mail-out" groups, respectively (3.17% and 3.20% using the Gail model). Hypothesis testing of the difference between cohort means showed that the mean risks of the cohorts were not significantly different within the risk assessment models (two sample z test, $P = 0.29$, Tyrer–Cuzick model; $P = 0.54$, Gail model).

The 4,266 women included in the final analysis were between the ages of 40 years and 79 years, with a mean age of 56.6 years (SD, 9.6 years). Respondents had an age distribution similar to that of both BC residents and women in the Screening Mammography Program (Fig. 1A). The predominant ethnicity of the survey population was reported to be British/Irish/Scottish/Welsh (54% of respondents; Fig. 1B); in the 2006 census, 49% of BC residents were self-identified as being of similar ethnicity (British Isles/European/English/Scottish/Canadian/Irish/Welsh; ref. 30). Response modality varied by age, with younger women making greater use of the online survey interface and older women more inclined to return the questionnaire by mail (Supplementary Fig. S2). This has implications for the use of web-based technology in future studies; computer and tablet surveys may become a more effective modality for data collection, particularly when targeting the younger demographic.

Overall, the median 10-year risk for all respondents ages 40 to 79 years was found to be 2.63% [interquartile range (IQR), 1.66%] using the Tyrer–Cuzick model and 2.86% (IQR, 1.41%) using the Gail model (Table 1). For women more than the age of 50 years, the median 10-year Gail risk was slightly higher than the median 10-year Tyrer–Cuzick risk. However, the Tyrer–Cuzick model found 3.5% of all respondents in this study population to be at high breast cancer risk, whereas only 1.1% of the study population was considered to be at high risk using the Gail model (Fig. 2). When the risk estimates generated by the two models were directly compared, some respondents at high 10-year risk according to one model were not necessarily considered to be high risk by the other model (Fig. 3). Specifically, 134 women in the study population (3.1%) were identified as high risk only by the Tyrer–Cuzick model, and 32 women (0.8%) were identified as high risk only by the Gail model. Seventeen women (0.4%) were considered to be high risk by both models. However, the two sets of assigned 10-year risks showed a greater correlation (Pearson correlation coefficient, $r = 0.54$) than the lifetime risk results found by Quante and colleagues ($r = 0.34$; ref. 12), indicating that the risk computations of the two models show stronger association for 10-year risk than lifetime risk. One reason for this could be that the Gail model accounts for competing risks of mortality other than breast cancer, whereas the Tyrer–Cuzick model (Version 6.0) does not (31). Competing mortality becomes more important when the risk is projected over increasingly long intervals, as is often the case when computing lifetime breast cancer risk.

Although the Tyrer–Cuzick model is considered to be the most comprehensive and accurate risk assessment model to date, to our knowledge, it has not yet been validated in the BC population. Another limitation of this study is the relatively small sample size. As a result, the populations of interest, specifically women at high risk of developing cancer and/or carriers of *BRCA1/2* mutations, are few in number. Thus, it is difficult to evaluate the calibration of risk assessment models in the upper tail of the risk distribution; there may be substantial uncertainty in the estimates of number of truly high-risk women in the general screening population. Although we attempted to recruit women from all geographic areas of BC, enrolment was disproportionate from the various sites and screening locations, and not all the cities across BC were represented in this study. Even so, the results should remain valid and applicable, with the risk distribution being representative

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

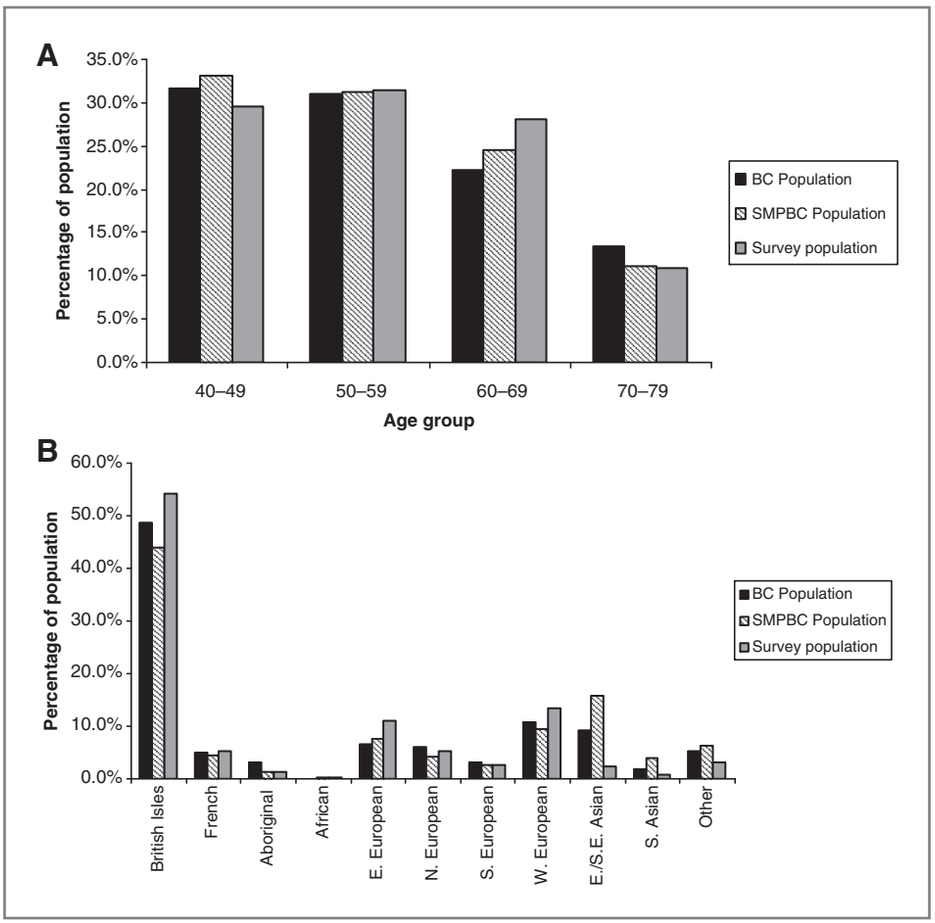


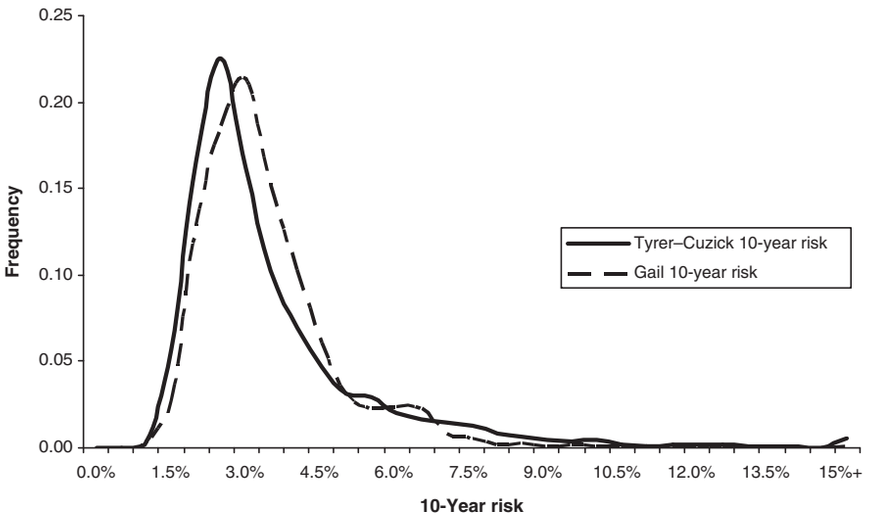
Figure 1. (A) age distribution and (B) ethnic distribution of women in three groups: British Columbia residents ages 40 to 79 years, women enrolled in the SMPBC, and women in the survey population.

of large areas of BC in which most of the population resides. The majority of the surveys were returned from women attending screening centers in Vancouver, Victoria, and Kelowna, three of the largest metropolitan areas by population in BC (32). Women typically self-enroll for screening mammography, and it has been shown that screening participants in the SMPBC have lower mortality rates for most cancer types than nonparticipants (33). Thus, it could be speculated that screening participants as a whole may exhibit different characteristics than the general female population of BC, including heightened health-related conscientiousness and increased use of medical services. In addition, women perceiving themselves to be at high breast cancer risk (such as those with a strong family history of cancer) may have been more motivated to respond to the survey, leading to potentially increased risk estimates (34). If additional MRI screening was implemented for high-risk women in the BC population, it would be these same women already in the SMPBC who would likely use these services.

Table 1. Summary statistics of the 10-year risk distributions for women in each age cohort, based on outputs computed by the Tyrer–Cuzick and Gail risk assessment models

	Tyrer–Cuzick 10-year risk					Gail 10-year risk				
Age group	Median	IQR	90th Percentile	95th Percentile	99th Percentile	Median	IQR	90th Percentile	95th Percentile	99th Percentile
40–49	2.35%	1.35%	4.99%	5.91%	10.32%	2.12%	0.79%	3.38%	3.84%	4.95%
50–59	2.72%	1.62%	5.90%	7.25%	10.76%	2.84%	1.03%	4.77%	5.35%	6.50%
60–69	2.76%	1.77%	6.13%	7.65%	12.03%	3.54%	1.40%	6.06%	6.72%	9.61%
70–79	2.93%	1.81%	6.52%	8.21%	16.42%	3.30%	1.40%	5.74%	6.53%	8.80%
40–79 (all women)	2.63%	1.66%	5.65%	7.22%	12.00%	2.86%	1.41%	4.93%	5.98%	8.35%

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027



10-Year risk threshold	Tyrer–Cuzick Model		Gail Model	
	Number	% of Sample	Number	% of Sample
% Low risk (< 3%)	2,607	61.4%	2,372	55.9%
% Moderate risk (3–8%)	1,508	35.1%	1,845	43.0%
% High risk (>8%)	151	3.5%	49	1.1%

Figure 2. Comparison of the 10-year risk distributions for all women ages 40 to 79 years in the survey population, as estimated by the Tyrer–Cuzick and Gail risk assessment models.

Nonetheless, the results of this study are in line with similar risk assessments undertaken by other groups. A study conducted by Evans and colleagues (23) in the United Kingdom used the Tyrer–Cuzick model to assess breast cancer risk, finding the median 10-year risk of women ages 45 years and older to be 2.65% with an IQR of 2.10%–3.45%. This is remarkably similar to the median 10-year Tyrer–Cuzick risk of 2.63% for women in this study and median Gail risk of 2.86% (Table 1). The same study by Evans and colleagues found that 1.07% of women in the United Kingdom had a 10-year breast cancer risk of 8% or more. In another risk assessment study using the Gail model, Graubard and colleagues (22) estimated that 1.09% of women in the United States between the ages of 30 and 84 years were at high lifetime risk of developing breast cancer. It has been noted that the Gail model may underpredict breast cancer risk, as it does not include family history of breast or ovarian cancer in second-degree relatives (35), whereas the Tyrer–Cuzick model incorporates extensive genetic and family history and may provide more accurate risk estimations (36). A recent evaluation of model performance by Quante and colleagues (12) found mean 10-year Gail and Tyrer–Cuzick risks of 3.18% and 5.49%, respectively. The mean 10-year Gail risk in this study was also 3.18%, and the mean Tyrer–Cuzick risk was 3.28%, somewhat lower than the estimate by Quante and colleagues. One potential reason for the Tyrer–Cuzick discrepancy could be that the current study population contained very few *BRCA1/2*-positive women (only 3 of the 4,266 respondents), whereas 5.9% of participants in the study by Quante and colleagues were *BRCA*-positive.

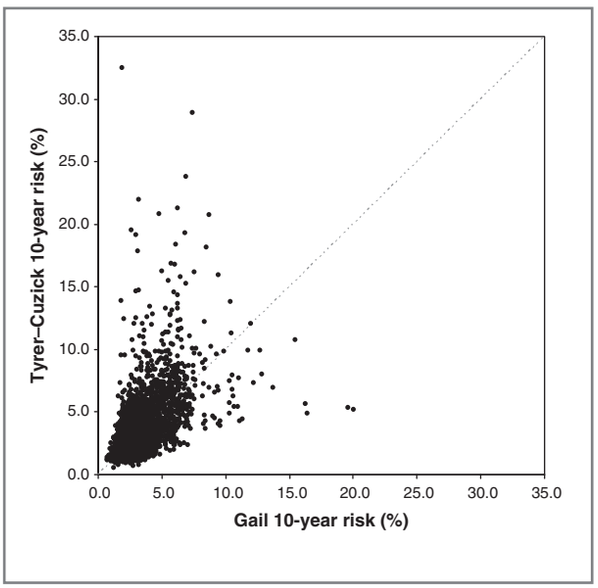


Figure 3. Scatterplot of Tyrer–Cuzick and Gail 10-year risk estimates for each of the 4,266 women in the study sample (Pearson correlation coefficient, $r = 0.54$).

Of the 4,266 women in the study sample, 151 women (3.5%) were found to be at high 10-year risk of developing breast cancer using the Tyrer–Cuzick model (Table 2). A critical analysis of risk factors by the Breast Cancer

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

Table 2. Characteristics of the 151 women in this study classified as having high risk of developing breast cancer (>8% 10-year risk) using the Tyrer–Cuzick model, compared with those not at high risk of breast cancer (≤8% 10-year risk)

Characteristics	High-risk women	Non-high–risk women
Number	151	4115
Age group		
40–49	19.2%	29.9%
50–59	31.1%	31.4%
60–69	31.8%	28.0%
70–79	17.9%	10.6%
Median age, y (SD)	59 (9.8)	56 (9.6)
BMI		
<25	40.9%	50.2%
≥25	59.1%	49.8%
Biopsy findings		
Previous biopsy	29.1%	16.1%
Hyperplasia	2.6%	0.5%
Atypical hyperplasia	4.0%	0.0%
LCIS	1.3%	0.0%
Personal cancer history		
Ovarian cancer	2.6%	0.7%
Genetic testing		
BRCA1/2-positive	2.0%	0.0%
Results pending	2.0%	0.2%
Ashkenazi inheritance	3.3%	1.2%
Reproductive history		
Age at menarche ≤11	22.5%	17.0%
Age at menopause ≥55	15.9%	7.8%
Nulliparous	30.9%	19.6%
First birth age <20	0.7%	7.6%
First birth age ≥30	26.8%	20.2%
Mean age first birth, y (SD)	28.4 (5.1)	26.1 (5.4)
HRT use		
Current HRT user	15.9%	9.5%
Estrogen-only	70.8%	53.6%
Combined	29.2%	46.4%
Mean length of time on HRT, y (SD)	19.8 (12.9)	9.2 (8.1)
Family cancer history		
≥1 first-degree relative[a] with:		
Breast cancer	83.4%	12.0%
Bilateral breast cancer	25.2%	0.6%
Ovarian cancer	5.3%	3.0%
Both breast and ovarian cancer	2.6%	0.2%
Breast/bilateral breast cancer diagnosis age <50	28.5%	4.3%
≥1 relative[b] with:		
Breast cancer	94.0%	32.0%
Bilateral breast cancer	35.1%	3.5%
Ovarian cancer	11.3%	8.3%
Both breast and ovarian cancer	10.6%	3.1%
Breast/bilateral breast cancer diagnosis age <50	38.4%	9.3%
Relatives per respondent:		
Diagnosed with cancer[c]		
Mean number (SD)	3.2 (2.1)	2.3 (1.8)
Range	1–13	1–16
Diagnosed with breast cancer (including bilateral)		
Mean number (SD)	2.1 (1.2)	1.4 (0.7)
Range	1–8	1–6
Percent Eligible:		
For MRI screening (*BRCA1/2* criteria)	2.6%	0.1%
For referral to HCP	30.5%	6.1%

Abbreviation: HCP, Hereditary Cancer Program.

[a]First-degree relatives include parents, siblings, and children.

[b]Second- and third-degree relatives also include grandparents, aunts, uncles, cousins, and grandchildren.

[c]Types of cancer included breast, bilateral breast, ovarian, and other (i.e., prostate, skin, gastrointestinal, lung, etc.).

Prevention Collaborative Group (3) described several factors significantly increasing breast cancer risk in postmenopausal women; a group of women that comprised 60% of the SMPBC study population. Among the high-priority risk factors were several that were surveyed in the current study, including Gail parameters, parity, number of children, age at menopause, BMI, history of HRT, ovarian cancer, family breast cancer history, and age of cancer onset. Although women in the non-high–risk group had a greater range in the number of relatives with cancer (range 1–16), many of these diagnoses were cancers other than breast or ovarian cancer. Risk factors in the literature that were not addressed by the current study include breast density, socioeconomic status, oral contraceptive use, alcohol consumption, diet, and dynamic processes such as height loss and weight gain over time (3, 37). At present, many of these factors are not included as parameters in risk assessment models, although the discriminatory accuracy of the models may be improved with their incorporation (3).

On the basis of personal and family history alone, nearly one third of the high-risk women identified in this study (30.5%) would be eligible for referral to the BC Cancer Agency's Hereditary Cancer Program (HCP), where a counselor may recommend adjunct MRI screening, risk-reducing strategies, and/or genetic testing (38). If MRI screening was offered exclusively to *BRCA1/2*-positive women and their

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

untested first-degree relatives, only 4 (2.6%) of the 151 high-risk women would be eligible for MRI screening. Of the non-high–risk women, 6 (0.1%) would be recommended MRI on the basis of *BRCA1/2* mutation status of a first-degree relative and 253 (6.1%) would potentially qualify for referral to the HCP.

MRI resources

After accounting for the 24-month participation rate of 50.7% reported by the SMPBC (1), the number of women in the BC screening population at high breast cancer risk was calculated using the age-specific provincial population estimates (39). From the Tyrer–Cuzick risk estimates, the percentage of women at high 10-year risk in each age group was multiplied into the projected female population of British Columbia. Approximately 19,414 women attending screening in BC were estimated to be at high breast cancer risk and potentially eligible for MRI screening (Table 3). The MRI resources required to screen these high-risk women were calculated by assuming a rate of 1 MRI screen per year per woman. With the use of a dedicated breast MRI unit, approximately 10 women could be screened in an 8-hour day. Operating such an MRI machine for 14 hours per day would allow 4,393 women to be screened in 1 year; therefore adjunct screening of the 19,414 women at high risk in BC would require 4 to 5 (4.4) additional MRI machines. In comparison, 5,849 women were estimated to be at high risk using the Gail model, requiring 1 to 2 (1.4) additional MRI machines for adjunct screening.

Although the survey sample was composed of a greater proportion of Caucasian individuals and fewer Asian women than the SMPBC population (Fig. 1B), this has a limited impact on the Tyrer–Cuzick risk estimates as this model does not incorporate ethnicity into its risk computations. The Gail model, however, does account for ethnicity, and as Caucasian women are known to have a higher incidence of breast cancer than Asian women (40), the breast cancer risk in this survey population may potentially be overestimated relative to the risk of the SMPBC population as a whole. To address this possibility, calculations were conducted to evaluate the impact of differences in the ethnic distribution on the Gail risk estimates. Overall, it was estimated that 1.1% of women ages 40 to 79 years in the study population were at high breast cancer risk using the Gail model. This was equivalent to 6,296 women in the screening program ages 40 to 79 years, requiring 1.4 additional MRI machines to screen these women. If the ethnic distribution was adjusted to approximate that of the SMPBC, by reducing the percentage of "Caucasian" women from 96.6% to 80.1% and increasing the percentages of "Chinese" women from 2.5% to 15.8% and "other Asian" women from 0.7% to 3.8%, it was estimated that 5,937 women would be at high risk, also necessitating 1.4 additional MRI machines. As a result, modifying the ethnic distribution of the survey sample to better approximate the ethnic distribution of the SMPBC did not impact MRI resources as per the Gail risk estimates. The large percentage listed as Caucasian in these calculations is due to the fact that the Gail model calculates Aboriginal and unspecified "other" ethnic groups as being of Caucasian ethnicity.

The full cost of acquiring these MRI machines will vary based on considerations such as the strength of the magnet, one-time set up and installation charges, and the potential use of mobile MRI units for screening women in rural and remote communities of BC. In practice, the actual number of MRI machines required may be fewer than estimated, as there tends to be low uptake to additional MRI screening procedures, even for women at high risk (25, 41). Factors such as claustrophobia, anxiety, time constraints, fear of injection or additional work-up, medical inability to tolerate the procedure (due to pacemaker, body habitus, or frail medical condition), and medical referring practices may contribute to the fact that only a small number of women undergo recommended breast MRI screening (42). Another important consideration is the cost effectiveness of screening high-risk women with adjunct MRI. Studies have shown that alternating MRI with mammography is typically cost effective for *BRCA1* mutation carriers (43), but there is little research addressing the use of

Table 3. Estimated number of high-risk women undergoing screening mammography in British Columbia and additional MRI resources required for adjunct screening of these women

	10-Year risk (Tyrer–Cuzick model)			10-Year risk (Gail model)		
	>8% risk threshold			>8% risk threshold		
Age group	% High risk	#BC women	#MRI	% High risk	#BC Women	#MRI
40–49	2.30%	4,070	0.9	0.16%	281	0.1
50–59	3.50%	6,061	1.4	0.75%	1,290	0.3
60–69	4.00%	4,962	1.1	2.41%	2,998	0.7
70–79	5.82%	4,321	1.0	1.72%	1,280	0.3
All women (40–79)		19,414	4.4		5,849	1.4

NOTE: Percentages of high-risk women are based on risk estimates from a sample of 4,266 women attending the Screening Mammography Program of British Columbia, using the NICE 10-year risk guidelines to evaluate the Tyrer–Cuzick and Gail models.

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

screening women considered to be at high risk based on risk assessment models. The cost effectiveness and cost of implementing MRI screening were outside the scope of this study, and have yet to be determined in full for high-risk women in the context of BC's provincial health care system. Undeniably, it is beneficial to limit MRI screening to smaller subgroups of the high-risk population, and future work will focus on evaluating the costs and benefits of various screening strategies. The results of this study can be used to inform decision-making groups about resource allocation for breast cancer screening in British Columbia. With these estimates of breast cancer risk, screening programs may be tailored to improve the early detection of breast cancer in high-risk women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Rajapakshe, P.B. Gordon
Development of methodology: R. Rajapakshe, C. Bitgood, C. Wilson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.R. Weisstock, R. Rajapakshe, C. Bitgood, C. Wilson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.R. Weisstock, R. Rajapakshe, C. Bitgood, A.J. Coldman, B.A. Parker
Writing, review, and/or revision of the manuscript: C.R. Weisstock, R. Rajapakshe, C. Bitgood, P.B. Gordon, B.A. Parker, C. Wilson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.R. Weisstock, C. Bitgood, S. McAvoy, A.J. Coldman, B.A. Parker
Study supervision: R. Rajapakshe

Acknowledgments

The authors thank the reviewers for their constructive comments, Dr. Jack Cuzick for providing the IBIS code, Dr. Elena Ostroumov for her help with preliminary data acquisition and quality analysis, Tanja Hoegg for assistance with statistical analysis, Chelsea Vandenberg and Krista Clement for their valuable input on the original manuscript, all the volunteer University of British Columbia Okanagan Campus students who helped distribute surveys at the SMPBC screening sites, and the study participants for their contributions to making this study possible.

Grant Support

This work was supported by funding from the Canadian Breast Cancer Foundation, BC Yukon Region, and the BC Cancer Foundation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 29, 2013; revised July 18, 2013; accepted August 1, 2013; published OnlineFirst August 20, 2013.

References

1. Screening Mammography Program of British Columbia. Screening Mammography Program 2011 annual report. BC Cancer Agency. 2011:1–58.
2. Singletary S. Rating the risk factors for breast cancer. Ann Surg 2003; 237:474–82.
3. Santen R, Boyd N, Chlebowski R, Cummings S, Cuzick J, Dowsett M, et al. Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model. Endocr Relat Cancer 2007;14:169–87.
4. Nelson H, Zakher B, Cantor A, Fu R, Griffin J, O'Meara E, et al. Risk factors for breast cancer for women aged 40 to 49 years. Ann Intern Med 2012;156:635–48.
5. Tyrer J, Duffy S, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23: 1111–30.
6. Gail M, Brinton L, Byar D, Corle D, Green S, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81:1879–86.
7. Claus E, Risch N, Thompson W. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 1991;48: 232–42.
8. Ford D, Easton D, Bishop D, Narod S, Goldgar D, the Breast Cancer Linkage Consortium. Risks of cancer in *BRCA1*-mutation carriers. Lancet. 1994;343:692–5.
9. Antoniou A, Pharoah P, Smith P, Easton D. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91:1580–90.
10. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998;62:145–58.
11. Amir E, Freedman O, Seruga B, Evans D. Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst 2010;102:680–91.
12. Quante A, Whittemore A, Shriver T, Strauch K, Terry M. Breast cancer risk assessment across the risk continuum: genetic and nongenetic risk factors contributing to differential model performance. Breast Cancer Res 2012;14:R144.
13. Saslow D, Boetes C, Burke W, Harms S, Leach M, Lehman C, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.
14. National Institute for Health and Care Excellence (2013) Clinical guideline 164: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. CG164. London: National Institute for Health and Care Excellence. 2013:1–57.
15. Cancerview.ca [Internet]. Breast cancer screening in Canada: key components for breast cancer screening programs/strategies across Canada [updated 2013 Apr 17, 2013; cited 2013 Jul 15, 2013]. Available from: www.cancerview.ca/cv/portal/Home/PreventionAndScreening/PSProfessionals/PSScreeningAndEarlyDiagnosis/BreastCancerScreening?_afrLoop = 240433351374000&_afrWindowMode = 0&_adf.ctrl-state = 19frlqkbi6_4.
16. Berg W, Zhang Z, Lehrer D, Jong R, Pisano E, Barr R, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. J Am Med Assoc 2012;307:1394–404.
17. Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, Konig R, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 2010;28:1450–7.
18. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: Using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 2008;148:671–9.
19. Granader E, Dwamena B, Carlos R. MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach. Acad Radiol 2008;15: 1590–5.
20. Elmore J, Barton M, Moceri V, Polk S, Arena P, Fletcher S. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998;338:1089–96.
21. McCann J, Stockton D, Godward S. Impact of false-positive mammography on subsequent screening attendance and risk of cancer. Breast Cancer Res 2002;4:R11.
22. Graubard B, Freedman A, Gail M. Five-year and lifetime risk of breast cancer among U.S. subpopulations: implications for magnetic

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

resonance imaging screening. Cancer Epidemiol Biomarkers Prev 2010;19:2430–6.
23. Evans D, Warwick J, Astley S, Stavrinos P, Sahin S, Ingham S, et al. Assessing individual breast cancer risk within the U.K. National Health Service breast screening program: a new paradigm for cancer prevention. Cancer Prev Res 2012;5:943–51.
24. Seyednoori T, Pakseresht S, Roushan Z. Risk of developing breast cancer by utilizing Gail model. Women Health 2012;52:391–402.
25. Brinton J, Barke L, Freivogel M, Jackson S, O'Donnell C, Glueck D. Breast cancer risk assessment in 64,659 women at a single high-volume mammography clinic. Acad Radiol 2012;19:95–9.
26. Breast Cancer Risk Assessment Project [Internet]. c2013 [updated 2012; cited 2013 Jul 15]. Available from: www.breastcancerrisk.ca.
27. IBIS Breast Cancer Risk Evaluation Tool [Internet] [updated 2013 June 20; cited 2013 Jul 15]. Available from: www.ems-trials.org/riskevaluator.
28. Breast Cancer Risk Assessment Tool [Internet] [updated 2011 May 16; cited 2013 Jul 15] Available from: www.cancer.gov/bcrisktool/Default.aspx.
29. Breast Cancer Risk Assessment Macro [Internet] [updated Dec 2012; cited 2013 Jul 15] Available from: dceg.cancer.gov/tools/risk-assessment/bcrasasmacro.
30. Statistics Canada [Internet]. Population by selected ethnic origins, by province and territory (2006 Census); [updated 2009 Jul 28; cited 2013 Jul 15]. Available from: www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo26k-eng.htm.
31. Gail M, Mai P. Comparing breast cancer risk assessment models. J Natl Cancer Inst 2010;102:665–8.
32. Statistics Canada [Internet]. Population and dwelling counts, for Canada, provinces and territories, census metropolitan areas and census agglomerations, 2001 and 1996 Censuses [updated 2001; cited 2013 Jul 15]. Available from: www12.statcan.ca/english/census01/products/standard/popdwell/Table-CMA-P.cfm?T=1&SR=1&PR=59&S=3&O=D.
33. Phillips N, Coldman A. Comparison of nonbreast cancer incidence, survival and mortality between breast screening program participants and nonparticipants. Int J Cancer 2008;122:197–201.
34. Katapodi M, Lee K, Facione N, Dodd M. Predictors of perceived breast cancer risk and the relation between perceived risk and breast cancer screening: a meta-analytic review. Prev Med 2004;38:388–402.
35. Ward E, Smith R. Integrating tools for breast cancer risk assessment, risk reduction, and early detection. Cancer Epidemiol Biomarkers Prev 2010;19:2428–9.
36. Evans D, Howell A. Breast cancer risk-assessment models. Breast Cancer Res 2007;9:213–20.
37. McPherson K, Steel C, Dixon J. Breast cancer - epidemiology, risk factors, and genetics. Br Med J 2000;321:624–8.
38. BC Cancer Agency [Internet]. Hereditary Cancer Program. c2012 [Updated 2013 May 22; cited 2013 July 15]. Available from: www.screeningbc.ca/Hereditary/GetReferral/Default.htm.
39. BC Stats [Internet]. Population by age and sex: B.C. and other provincial and territorial populations: 1971–2012 (July 1); c2013 [updated January 2013; cited 2013 Jul 15]. Available from: www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx.
40. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe H, et al. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006;56:168–83.
41. Berg W, Blume J, Cormack J, Mendelson E, Lehrer D, Bohm-Velez M, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. J Am Med Assoc 2008;299:2151–63.
42. Berg W, Blume J, Adams A, Jong R, Barr R, Lehrer D, et al. Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666. Radiology 2010;254:79–87.
43. Cott C, Lee J, Gilmore M, Kong C, Lowry K, Halpern E, et al. Cost-effectiveness of alternating magnetic resonance imaging and digital mammography screening in BRCA1 and BRCA2 gene mutation carriers. Cancer 2012;119:1266–76.

Published OnlineFirst August 20, 2013; DOI: 10.1158/1940-6207.CAPR-13-0027

Cancer Prevention Research

Assessing the Breast Cancer Risk Distribution for Women Undergoing Screening in British Columbia

Christina R. Weisstock, Rasika Rajapakshe, Christabelle Bitgood, et al.

Cancer Prev Res 2013;6:1084-1092. Published OnlineFirst August 20, 2013.