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A Microsimulation Model for Evaluating the Effectiveness of Cancer Risk Management for *BRCA* Pathogenic Variant Carriers: miBRovaCAre

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ABSTRACT

Objectives: To develop a validated model for evaluating the real-world effectiveness of long-term clinical management strategies for women with germline *BRCA1* or *BRCA2* pathogenic variants.

Methods: A microsimulation model was developed that included a *BRCA*-specific natural history for breast and ovarian cancer, a clinical framework for carrier follow-up, and cancer risk management strategies (breast screening, risk-reducing mastectomy, and bilateral salpingo-oophorectomy). Adherence rates and outcomes for breast screening and risk-reducing surgery were obtained from *BRCA* carriers seen through a familial cancer service in Melbourne, Australia. The model was assessed for internal and external validity. The model was used to compare women perfectly adhering to screening recommendations versus actual adherence of the clinical cohort.

Results: The model accurately predicted cancer incidence, pathology, and mortality. Using actual adherence for breast screening resulted in additional breast cancer deaths (per 1000 women: *BRCA1*, 2.7; *BRCA2*, 1.6) compared with perfect screening adherence. This decreased average life expectancy by 0.30 life-years for *BRCA1* and 0.07 life-years for *BRCA2*. When carriers had access to risk-reducing mastectomy, the benefit from improved screening adherence was not significant.

Conclusions: The developed model is a good descriptor of *BRCA* carriers' lifetime trajectory and its modification by use of risk management strategies alone or in combination. Evaluations of breast screening in *BRCA* carriers may overestimate the benefits of screening programs unless adherence is considered. By incorporating real-world clinical practice and patient behavior, this model can assist in developing clinical services and improving clinical outcomes for carriers.

Keywords: *BRCA*, prevention, screening, simulation.

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Introduction

Pathogenic variants (PVs) in *BRCA1* and *BRCA2* confer an increased absolute lifetime risk of breast and ovarian cancer, from 45% to 65% and from 11% to 39%, respectively.[1] *BRCA*-associated cancers commonly have features associated with a poorer prognosis, including a young age of onset, high tumor grade, and a large proportion of breast cancers being hormone receptor–negative.[2]

Women who are aware of their high-risk *BRCA* PV status can access strategies for cancer prevention and early detection.[3] Recommended cancer risk management includes risk-reducing bilateral salpingo-oophorectomy (RRBSO), contralateral and bilateral prophylactic mastectomy (CPM and BPM), and intensive breast screening using annual mammography and breast magnetic resonance imaging (MRI) from a young age.[4-6] There is a proven survival benefit in the case of RRBSO.[7] BPM and CPM are effective in reducing breast cancer risk, although any improvement in overall survival has not yet been established.[8] Similarly, annual mammography and MRI result in early detection of cancer before it has spread to lymph nodes or distant tissues (downstaging), but its impact on survival for *BRCA* carriers is unclear.[9-11] Ovarian cancer screening is currently not recommended because of insufficient evidence for either downstaging or mortality reduction.[12]

Long-term prospective studies examining the overall benefit of these strategies, alone and in combination, are expensive and challenging, given the rarity of germline *BRCA* PV in the

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population and lengthy follow-up time required. The increasing affordability of genetic testing (GT) and the rise of personalized medicine are all contributing to the ascertainment of more *BRCA* carriers.[13] Nevertheless, there are minimal empirical data on the outcomes of long-term clinical management of carriers once their genetic status is known. Although the clinical effectiveness of individual risk management strategies is comparatively well studied, there has been less focus on how to manage the overall care of these high-risk women and integrating the use of strategies over time so that they undergo suitable risk management at the appropriate time, given their age and life stage. The provision and delivery of healthcare services is crucial to optimize appropriate and timely risk management, but is susceptible to competing demands; therefore, robust data supporting risk management strategies are essential to ensure adequate healthcare services for carriers.

Carriers' adherence behavior affects the utility of management strategies in mitigating the effects of *BRCA* PVs, but it is also important information for healthcare providers and funders. For example, adherence to breast screening has been shown to be an important consideration for decision making regarding the effectiveness and cost-effectiveness of breast screening interventions.[14] One approach to improve adherence rates is to use a specialist multidisciplinary clinic. Familial cancer services (FCSs) are specialist clinics that assist in the identification and ongoing care of individuals and families who are at increased risk of cancer because of a hereditary predisposition.[15,16] The introduction of an FCS has been shown to increase both referral of patients eligible for GT and adherence to cancer risk management guidelines.[16-18] Lower adherence to risk management guidelines has been reported when women are left to arrange their own care,[18,19] partly attributable to a lack of awareness of guidelines.[20,21]

Decision modeling can be a useful tool in the absence of empirical data to determine the context and means by which *BRCA* carriers should be managed and to prioritize clinical areas (screening, risk-reducing strategies, or behavior modification) for the most consistent and optimal care of these women. There are numerous decision models investigating breast screening, prophylactic surgery, risk-reducing medication (RRM), or a combination of these strategies, among *BRCA* carriers.[22] Nevertheless, the inputs used in these models are frequently inappropriate, such as those extrapolated from values in the general population, or where *BRCA1* and *BRCA2* carriers are analyzed together as a homogeneous group. There are significant differences in natural history between the genes, including baseline cancer risks, and the overrepresentation of the aggressive triple-negative (TN) phenotype (estrogen, progesterone receptor negative, and HER2 unamplified) in *BRCA1*-associated breast cancer.[2] A major limitation of existing studies is that women's adherence to risk management recommendations is commonly assumed to be perfect or near perfect, poorly reflecting actual behavior. None consider the resources required to maintain effective uptake of risk management strategies over many years or refer to any clinical framework through which *BRCA* carriers are managed and strategies are accessed.

In the present study, we aimed to develop a model for *BRCA1* and *BRCA2* carriers for predicting the long-term effectiveness and cost-effectiveness of integrating a range of risk management strategies. This is the first model that combines a gene-specific model of disease with longitudinal data from a clinical cohort to reflect real-world participation and adherence to cancer risk management strategies in a supported clinical setting and the impact this has on long-term outcomes for *BRCA* carriers.

Methods

Study Population

Data were obtained from medical records for women with a germline PV in *BRCA1* or *BRCA2* seen at a single specialized cancer center in Melbourne, Australia. The study protocol was approved by the local institutional review board. Participants were excluded if they (1) carried more than 1 cancer-predisposing PV (n = 4), (2) previously declined participation for all research (n = 4), (3) were aged 70 years or older at GT (n = 4), or (4) died before receiving GT results (n = 31). The data set included both retrospective data (pre-GT) and prospectively collected clinical data (post-GT) for cancer diagnoses, risk management uptake, and clinic attendances between October 1996 and March 2017. Of the 1026 women considered for inclusion, 983 were eligible. The characteristics of the study population are presented in Table 1.

Model Structure

The model, miBRovaCAre, was coded in Python version 3.6 (Python Software Foundation, Wilmington, DE) and involved a discrete-time state-based microsimulation, with a lifetime time horizon and annual cycles. The model was structured around a core natural history module that predicted the onset, characteristics, and outcomes for breast and ovarian cancer in the absence of intervention. The natural history contained parameters specific for *BRCA1* and *BRCA2* carriers because of significant differences in disease presentation compared with the general population.[2] A microsimulation model was used instead of a memoryless Markov cohort approach for several reasons. The first related to the time dependency of several health states, including the change in cancer-specific mortality over time, and the time-dependent transition of preclinical to clinically diagnosed breast cancer. Second, the clinical effectiveness of breast screening was dependent on the assumption of improved prognosis because of the downstaging of tumors through early detection, which in a cohort-based model required many additional health states to capture differences in important prognostic markers (cancer stage, grade, and hormone receptors). Previous events also affected future adherence rates, meaning individual tracking variables were needed. Finally, microsimulation was thought to allow more flexibility for updating to incorporate new evidence, and to apply to other patient groups and interventions in the future. A detailed overview of miBRovaCAre is provided in the Model Overview section and Appendix Figures 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008.

All individuals entered the model at the age of 20 years, with no personal history of cancer and no previous risk management. The FCS intervention included modules for breast screening, risk-reducing surgery, and clinical follow-up events such as clinic appointments and specialist review. Parameters for clinical effectiveness, uptake, and adherence were included. Risk management options were mammogram, breast MRI, RRBSO, BPM, and CPM. Uptake of risk management procedures and clinic attendance was determined stochastically at the beginning of every cycle and was affected by an individual's age, gene, previous clinic attendance, and personal cancer history. Further information and a list of modeling assumptions are provided in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008.

Cancer Onset and Clinical Diagnosis

The natural history model predicted the onset of ovarian and preclinical breast cancer in the absence of screening or surgery, and the time from onset to clinical presentation because of

Table 1. Study population.

Parameters	*BRCA1* carriers (n = 491)	*BRCA2* carriers (n = 492)
Unaffected at GT	n = 224	n = 269
Age at GT (y)		
Mean	36.43	39.05
Median (IQR)	33.71 (26.46-44.92)	36.08 (28.54-47.21)
Follow-up time (y)		
Mean	5.55	6.42
Median (IQR)	6.57 (2.68-9.89)	5.86 (2.57-9.66)
Age at BC diagnosis (during follow-up)	n = 27	n = 34
Mean	42.07	49.41
Median (IQR)	38 (35.5-38)	46.5 (40-55)
RRBSO uptake, all ages	94/224 (41.96%)	114/269 (42.38%)
RRBSO uptake, age >45 y	60/82 (73.17%)	94/126 (74.60%)
Age at RRBSO		
Mean	45.13	48.20
Median (IQR)	43.85 (38.50-48.28)	45.32 (42.72-52.00)
BPM uptake, all ages	70/224 (31.25%)	66/269 (24.54%)
Age at BPM		
Mean	38.86	39.04
Median (IQR)	38.01 (33.51-43.59)	38.13 (33.61-44.43)
Women with unilateral BC at GT	n = 152	n = 150
Age at GT (y)		
Mean	46.52	48.92
Median (IQR)	45.30 (38.97-52.12)	48.07 (41.84-56.30)
Follow-up time (y)		
Mean	6.33	5.68
Median (IQR)	5.19 (2.32-10.16)	3.67 (1.37-9.40)
Age at first BC diagnosis (before GT)		
Mean	42.19	44.51
Median (IQR)	41.44 (35.09-47.87)	44.31 (37.47-50.45)
RRBSO uptake, all ages	99/152 (65.13%)	88/150 (58.67%)
RRBSO uptake, age >45 y	85/116 (73.28%)	76/115 (66.09%)
Age at RRBSO		
Mean	48.48	49.70
Median (IQR)	46.82 (42.36-53.82)	49.18 (44.25-55.65)
CPM uptake	77/152 (40.66%)	73/150 (48.67%)

BC indicates breast cancer; BPM, bilateral prophylactic mastectomy; CPM, contralateral prophylactic mastectomy; GT, genetic testing; IQR, interquartile range; RRBSO, risk-reducing bilateral salpingo-oophorectomy.

symptomatic disease (breast cancer only). Key input parameters are provided in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008. Lifetime cancer risks were based on age- and gene-specific cumulative incidence from a prospective cohort of *BRCA* carriers.[1]

The onset of ovarian cancer was assumed to be the time of clinical (symptomatic) detection, because evidence indicates that the screen-detectable period may be as short as a matter of months, and ovarian cancer screening is not proven to be effective for early detection.[12,23] In contrast, breast cancer onset was the time of initiation of preclinical breast cancer, which is asymptomatic and detectable via mammography and/or MRI. Tumor growth of breast cancer was not directly modeled, and cancers were instead assigned a preclinical sojourn time using previously published estimates to account for the fast-growing nature of *BRCA*-associated cancer.[24] In the absence of screening, breast cancer was assumed to be diagnosed once the time in the preclinical disease state exceeded the sojourn time, when the patient would present for clinical investigations upon becoming symptomatic.

Cancer Pathology

Cancer pathology features were assigned stochastically after clinical diagnosis and were dependent on age (<55 or ≥55 years for breast cancer) and detection mode. Breast cancer attributes included tumor size, lymph nodes, metastasis, estrogen, progesterone, and HER2 status. The probabilities for each feature were calculated using subsets of participants from the study population (see the Model Overview section in Supplemental Materials). Screen-detected cancers and occult cancers found on prophylactic mastectomy were smaller and less likely to have spread to lymph nodes or have distant metastases (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008).

Ovarian cancers were categorized by summary stage (local, regional, or distant) and were dependent on whether detection was symptomatic[25] or through RRBSO histopathology[12,26-28] (see Appendix Table 2 in Supplemental Materials).

Mortality

Competing mortality was based on other-cause mortality from Australian life tables after excluding breast and ovarian cancer deaths.[29,30] Women who underwent premenopausal RRBSO, defined as before the age of 45 years, were assumed to have a 3% increased risk of mortality because of cardiovascular disease.[31]

Individuals were at risk of cancer-specific death up to 10 years after diagnosis. Ovarian cancer survival was stage-, age-, and gene-specific. A time-varying Cox proportional hazard model developed

from a meta-analysis of patients with *BRCA1*- and *BRCA2*-associated ovarian cancer was applied to relative survival data for local disease from the Surveillance, Epidemiology and End Results program.[25,32]

The debate on the mortality outcomes of *BRCA*-associated breast cancer compared with sporadic cases is ongoing.[33] We assumed breast cancer mortality to be the same as the general breast cancer population after accounting for prognostic features, including those common in *BRCA*-associated cancers (see the Model Overview section in Supplemental Materials).[32,34]

Breast Screening and Risk-Reducing Surgery Component

The interventional component included multidisciplinary cancer risk management clinic attendance, breast screening, BPM, CPM, and RRBSO. Clinical pathways for standard care were based on Australian clinical guidelines and expert opinion and were dependent on age, gene, and personal cancer history.[4] Uptake probabilities were obtained from the study cohort to evaluate the actual impact of current risk management adherence rates.

Individuals were assigned an age at first MRI and mammogram, on the basis of initial uptake of screening by *BRCA* carriers in the study cohort (details are provided in the Model Overview section in Supplemental Materials). The median age at first screen was 30.1 years for mammogram and 27.3 years for MRI, with no significant difference detected between *BRCA1* and *BRCA2* (see Appendix Table 3 and Figure 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008).

The probability that a woman was perfectly adherent to ongoing annual breast screening in any given cycle was based on the proportion of *BRCA* carriers who attended a screening examination within 13 months of their previous examination (77.7% if aged <40 years and 93.3% if aged ≥40 years; see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008). Women not perfectly adherent were assigned a time to next screen during each cycle, which was dependent on enrollment in a cancer risk management clinic, and whether the woman was of childbearing potential (aged <40 years, a factor known to increase intervals between screening rounds[20]). For modeled individuals in a preclinical breast cancer health state, if the sojourn time expired before the assigned screening month, she would be diagnosed with a symptomatic interval breast cancer and the routine breast imaging would not occur. A delay in screening therefore increased the likelihood of being diagnosed at a more advanced stage (poorer prognosis).

Guidelines recommend RRBSO on completion of childbearing from the age of 35 years for *BRCA1* and from the age of 40 years for *BRCA2*.[4] Age-specific RRBSO uptake probabilities were obtained from the study cohort, stratified by gene (see the Material Model Overview section and Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008). Overall uptake in at-risk women in the study cohort was 76.7% (95% confidence interval [CI] 62.5%-90.2%) for *BRCA1* and 70.2% (95% CI 53.4%-85.4%) for *BRCA2* (see Appendix Figure 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008). Probabilities for BPM/CPM uptake were similarly calculated on the basis of subsets of the study cohort as described in the Model Overview section in Supplemental Materials. By the age of 40 years, 63.2% (95% CI 47.8%-74.1%) of at-risk *BRCA1* carriers and 64.9% (95% CI 49.0%-75.9%) of *BRCA2* carriers had undergone BPM (see Appendix Figure 4 in Supplemental Materials). Only 65.6% of carriers had a CPM within a year of their first breast cancer diagnosis.

Clinical effectiveness for cancer risk reductions for BPM, RRBSO, and CPM was from recent meta-analyses (see Appendix Table 3 in Supplemental Materials).[7,35,36] After controversy over evidence for a breast cancer risk reduction from RRBSO in premenopausal *BRCA1* carriers, an assumption of no effect on subsequent breast cancer risk was made.[37,38]

Sensitivity and specificity for mammogram, MRI, and combined modality (mammogram/MRI) are gene-specific and differ between prevalent and subsequent screening rounds (see Appendix Table 3 in Supplemental Materials).[39] There is no empirical evidence of improved survival in *BRCA* carriers undergoing annual breast screening, meaning any mortality benefit is a result of stage shift in screen-detected cancers.[9]

Model Validation

Internal validation to test for coding accuracy and impact of model assumptions was performed.[40] The external validity of the model was assessed for cancer-specific mortality, mode of detection for breast cancer, and cancer pathology. The validation targets are described in the Model Overview section in Supplemental Materials.

Breast cancer pathology in the model was assigned differently according to the mode of detection, consequently affecting breast cancer survival. To test the assumptions relating to breast cancer onset, sojourn time, and diagnosis, the mode of detection predicted by the model was compared with observed prospective clinical data for unaffected *BRCA* carriers from the study population (see details in the Model Overview section in Supplemental Materials).

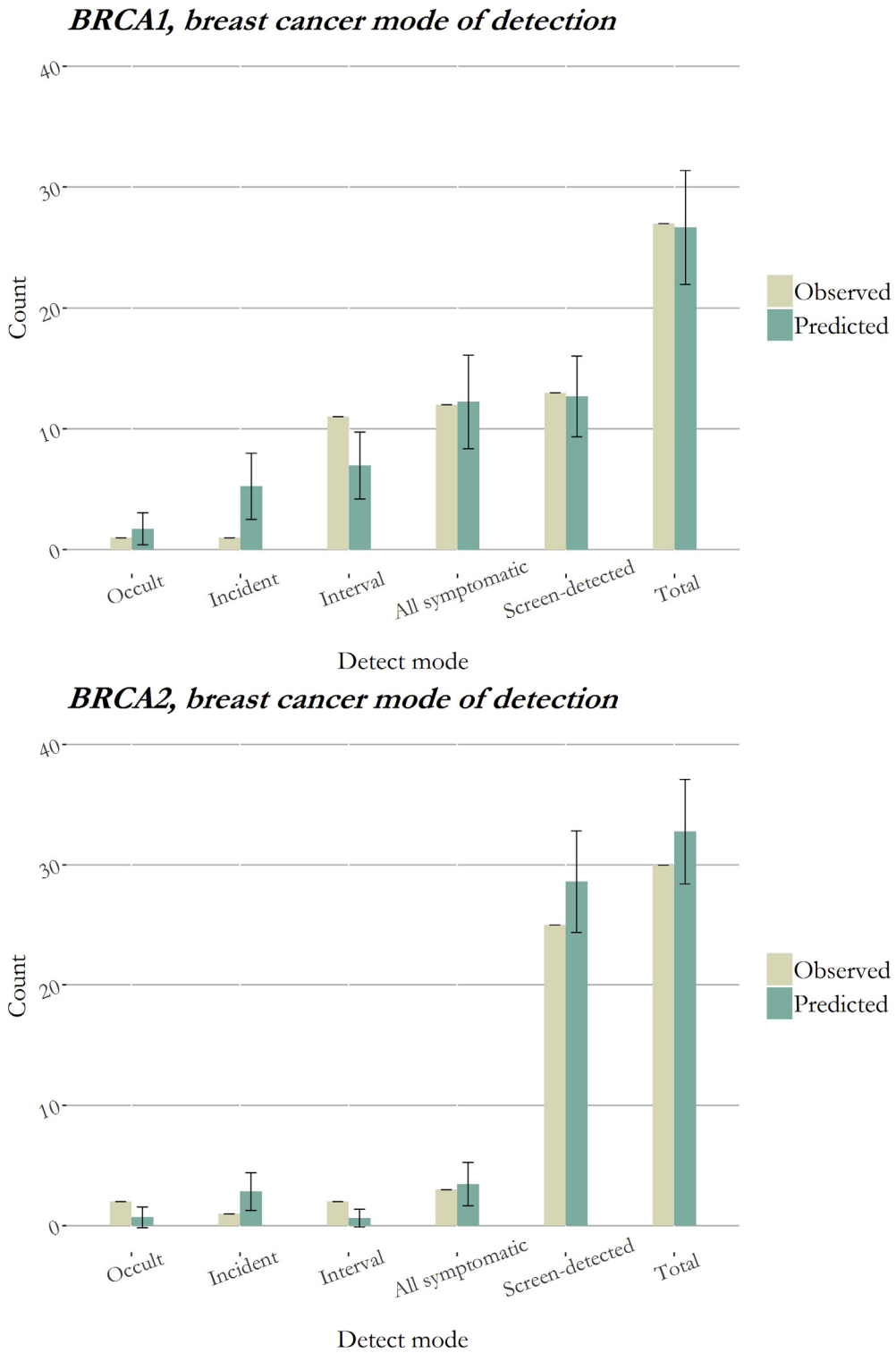
Breast Screening Adherence Scenario Analysis

The standalone effect of breast screening was chosen to illustrate the difference in clinical effectiveness when using real-world clinical data versus perfect adherence for predicting health outcomes and the relative value of focusing clinical resources on optimizing screening uptake. The hypothetical strategy of perfect adherence (optimal) to mammography/MRI was compared with the actual (suboptimal) attendance patterns of *BRCA* carriers in the study cohort as detailed earlier in the breast screening component and in Appendix Tables 3 and 4 in Supplemental Materials. Perfect adherence was defined as commencing MRI at the age of 25 years and mammogram at the age of 30 years, with all subsequent annual screens attended and on time. A comparator of no breast cancer screening was included. Individuals could undergo RRBSO in all scenarios, but scenarios were initially run excluding BPM and CPM to isolate the impact of screening. Outcomes included the number of invasive cancers prevented, screens performed, breast cancer deaths averted, and life expectancy. No discounting was applied because this was a validation study.

Statistical Analysis

Statistical analyses were carried out in R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). The proportional hazards assumption was tested using Schoenfeld residuals test. Categorical variables were compared using the Pearson χ^2 test for independence, or the Fisher exact test where any counts were less than 5. Student t test was used for continuous variables. Kaplan-Meier survival curves were compared using the log-rank test. A P value of less than .050 was considered statistically significant. For breast screening adherence, the length of time between screens was estimated using a generalized estimating equation with repeated attendances clustered for the same individual (244 individuals with 1041 observations).

Figure 1. Validation of mode of detection.



BRCA1 and BRCA2 breast cancer incidence and mode of detection were validated independently. The accuracy by which the model predicted the mode of detection was compared with outcomes of a prospectively followed clinical cohort. The number of cancers and the detection mode were well predicted by the model, with no significant difference in all simulations when classified as all-symptomatic, screen-detected, or occult. Definitions: Occult cancers were those diagnosed after prophylactic mastectomy. Incident cancers were symptomatically diagnosed cancers where the last screening examination was at least 13 mo before. Interval cancers were symptomatic cancers diagnosed within 12 mo of a normal breast screening examination. All-symptomatic represents combined interval and incident cancers. Screen-detected cancers were those diagnosed after an abnormal finding on breast MRI or mammography. MRI indicates magnetic resonance imaging.

Results

Model Validation

The validation results for cancer incidence and mortality are presented in Appendix Figure 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008 The predicted cumulative breast and ovarian cancer incidence in the absence of intervention was within age-specific 95% CIs for *BRCA1* and *BRCA2* in 100% of simulations. Breast cancer survival was externally validated against a fully independent prospective cohort of young-onset breast cancer cases (age ≤40 years) with a *BRCA* PV.[41] The model closely reproduced observed overall survival for women diagnosed with TN breast cancer. Overall survival for all breast and ovarian[42] cancers in *BRCA1* and *BRCA2* carriers was also reasonably reproduced, although predicted long-term survival trended slightly higher for breast cancer.

Spread to lymph nodes (node-positive) and TN status were validated because these features exerted a negative effect on breast cancer–specific survival in the model. Although mode of detection does not affect TN status, *BRCA* carriers who have their cancer detected on screening are less likely to have had the cancer spread to the lymphatic system[43] (present study data). No significant difference was found between the frequency of observed and predicted node-positive cases for both symptomatic and screen-detected diseases in 95% of *BRCA2* simulations and 91% of *BRCA1* simulations (see Appendix Figure 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008). Estrogen status, as a surrogate measure to categorize TN/non-TN breast cancers, was similarly reproduced.

The number of breast cancers diagnosed according to detection mode was validated using prospective clinical data. The model predicted a mean of 26.96 ± 4.71 diagnoses for *BRCA1* and 32.77 ± 4.36 for *BRCA2*, compared with 27 *BRCA1*- and 30 *BRCA2*-associated cancers observed during the follow-up period (Fig. 1). Both the number of cancers and detection mode were well predicted by the model, with no significant difference in 100% of simulations when cases were classified as symptomatic, screen-detected, or occult (on BPM). The model underpredicted interval symptomatic cancers (diagnosed between annual breast screens) and overpredicted incident symptomatic cancers (no recent screening) in *BRCA1* carriers in 39% of simulations, but because the same distribution of pathology characteristics was applied to all symptomatic cancers irrespective of arising as an interval or incident, this discrepancy did not affect other outcomes.

Impact of Actual Versus Perfect Screening Adherence

The validated model was used to examine the difference in health outcomes between no breast screening, suboptimal adherence, and optimal adherence to breast screening guidelines for *BRCA* carriers. Access to BPM/CPM was excluded in the primary analysis.

Outcomes for all scenarios are presented in Table 2. By the age of 45 years, 76.89% of *BRCA1* and 61.21% of *BRCA2* carriers had undergone RRBSO in the model. The hypothetical scenario of perfect breast screening adherence significantly increased life expectancy compared with running the model with the actual adherence rates obtained from clinical data. The difference was greater for *BRCA1* with 0.3 life-years saved, compared with *BRCA2* carriers with 0.07 life-years saved. The difference did not result from a change in breast cancer incidence, but instead from fewer cancers being diagnosed at an advanced stage and an associated decrease in breast cancer–specific mortality (breast cancer deaths averted per 1000 women: *BRCA1*, 33.67 suboptimal, 36.38 optimal; *BRCA2*, 65.18 suboptimal, 66.77 optimal). In the optimal scenario, 142 to 143 additional breast screening examinations were performed to avert a single breast cancer death. The difference between screening arms was minimal when BPM/CPM was introduced, because breast cancer incidence was significantly lowered, which even further prevented breast cancer–specific deaths.

Discussion

We have developed a validated microsimulation model for estimating the long-term outcomes for clinical management of *BRCA1* and *BRCA2* carriers using real-world data. The strength of this model lies in incorporating gene-specific natural histories and the effect of individuals' behavior (adherence) over time on the clinical effectiveness of cancer risk management recommendations for carriers overall. Compared with simpler cohort models, microsimulations can better represent the complexity in disease development and the heterogeneity in terms of both risk and behavior between individuals,[44] better reflecting real-life. This in turn more accurately describes the likely benefits of interventions overall, which can direct targeted studies to optimize adherence as well as more accurately guide workforce and healthcare resource planning.

A main advantage of the current model over previous published models is the use and validation of *BRCA*-specific parameters related to breast and ovarian cancer. For many models, whether a validation is performed, their results are frequently underreported.[45] This is particularly important in relation to breast cancer and the effect of screening because of the assumptions related to the unobservable aspects of cancer onset and progression. Input data were obtained from multiple sources because of the scarcity of information on *BRCA* carriers, particularly for natural history parameters. There is significant uncertainty around the preclinical phase of *BRCA*-associated breast and ovarian cancer. Evidence indicates that *BRCA*-associated tumors are more aggressive with a shorter screen-detectable period than the noncarriers,[24] but more detailed information on tumor growth and the rate of regional and distant metastasis is not available. Prospective breast cancer pathology data for noninterval, clinically detected disease are limited, because women who are aware of their *BRCA* PV status are overwhelmingly undergoing breast imaging or have had prophylactic mastectomy. We were fortunate to have access to a database of *BRCA* carriers with complete screening and cancer histories that could be combined with estimates from a previous calibrated model.[24] Our model was validated for breast and ovarian cancer mortality using independent published data. It was also validated against a prospective clinical cohort for breast cancer incidence and mode of detection. Model-predicted overall survival after a primary breast cancer diagnosis did trend higher for *BRCA1* and *BRCA2* in later years, potentially reflecting the lower uptake of RRBSO (9% vs 69% in the present study) and CPM (32% vs 65%) in the validation cohort. Validation against independent data was not possible in all cases because populations for international *BRCA* carrier cohort studies frequently overlap.

Breast screening scenarios with variable adherence were presented to demonstrate the impact of patients' behavior on long-term health outcomes, a factor not addressed in most models. This has implications for both current and future healthcare resource use. Although not included in the present study, there is likely to be substantial variation in healthcare costs resulting from the differences in the number of breast screens performed, as well as higher treatment costs for more advanced breast cancers.[46,47] Any significant benefit from increasing screening adherence is

Table 2. Impact of optimal and suboptimal compliance to breast cancer screening on model outcomes.

Variable	No screening	Suboptimal adherence	Optimal adherence	Suboptimal with BPM/CPM	*P* value
BRCA1 carriers					
Life expectancy	77.65	78.52	78.82	79.24	NoSc vs suboptimal: $P<.00001$ Suboptimal vs optimal: $P<.00001$ Suboptimal vs +BPM/CPM: $P<.00001$
Incremental LYS	3.44*	0.87	0.30	0.42	
Invasive cancer diagnoses (per 1000 person-years)	13.15	13.29	13.27	4.60	NoSc vs suboptimal: OR 1.01; $P=.420$ Suboptimal vs optimal: OR 1.00; $P=.500$ Suboptimal vs +BPM/CPM: OR 0.35; $P<.00001$
Breast cancer deaths (per 1000 women)	146.22	112.56	109.85	53.71	NoSc vs suboptimal: $P<.00001$ Suboptimal vs optimal: $P<.00001$
Number of screens per breast cancer death averted (vs NoSc)	–	1478	1621	186	
BRCA2 carriers					
Life expectancy	79.65	81.48	81.55	82.08	NoSc vs suboptimal: $P<.00001$ Suboptimal vs optimal: $P=.002$ Suboptimal vs +BPM/CPM: $P<.00001$
Incremental LYS	0.24*	1.83	0.07	0.53	
Invasive cancer diagnoses (per 1000 person-years)	9.88	9.55	9.55	4.55	NoSc vs suboptimal: OR 0.97; $P=.160$ Suboptimal vs optimal: OR 1.00; $P=.510$ Suboptimal vs +BPM/CPM: OR 0.48; $P<.00001$
Breast cancer deaths (per 1000 women)	153.02	87.84	86.25	49.57	NoSc vs suboptimal: $P<.00001$ Suboptimal vs optimal: $P<.00001$
Number of screens per breast cancer death averted (vs NoSc)	–	836	978	250	

Note. Statistical significance from Student *t* test for continuous variables and χ^2 test for categorical variables or rates.
BPM indicates bilateral prophylactic mastectomy; CPM, contralateral prophylactic mastectomy; LYS, life-years saved; MMG, mammogram; MRI, magnetic resonance imaging; NoSc, no screening; OR, odds ratio; RRBSO, risk-reducing bilateral salpingo-oophorectomy.
*Versus natural history (no RRBSO).

offset when allowing for access to prophylactic mastectomy, meaning that tracking of screening behavior is likely to be insignificant when evaluating the effectiveness of combined risk management strategies. Rates of adherence also improve significantly with age, meaning that outcomes will be different for women who enter the program later in life (see Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.008). These results emphasize that not considering attendance rates will overestimate the effectiveness of screening programs in evaluations of breast screening alone.[14] This is an important clinical issue because currently less than half of identified *BRCA* carriers undergo prophylactic mastectomy.[48,49] With current participation rates for risk management under the FCS clinical program, the average life expectancy of *BRCA* carriers still remains substantially lower than the general Australian population average of 84 years.[30]

Our model has several limitations. RRMs such as aromatase inhibitors and selective estrogen receptor modulators were not included. Nevertheless, uptake of RRM for primary breast cancer prevention is very low,[50] and evidence for efficacy of selective estrogen receptor modulators in *BRCA* carriers is lacking.[51] Second, surrogate outcomes were used for the breast cancer–specific survival associated with breast screening because of the absence of evidence for a direct mortality benefit.[9,11] By accounting for several prognostic indicators, as well as applying stage distributions from real-world clinical data, we hope to have minimized bias. Third, both the elements of the natural history and clinical intervention are primarily derived from white participants and it is likely that these inputs would need adjusting for different ethnic groups.[52]

Conclusions

We have developed a flexible and validated model for determining the effectiveness of integrated cancer risk management strategies for *BRCA* carriers. Services offering GT are proliferating, with population-based testing potentially available in the near future.[53,54] The value obtained from any GT primarily depends on whether it leads to behavior modification. A great deal of effort and resources are invested into defining and refining cancer risks associated with genetic predispositions, but outcomes are dependent on how individuals ultimately act on this information, and by extension how to best engage patients in their own care. Because GT for *BRCA1/2* began only in the mid-1990s, the long-term outcomes cannot be determined outside of modeling,

although there are studies underway.[55] Our study shows that data collected as part of routine clinical follow-up can be used for model-based evaluations of clinical programs and demonstrates the long-term benefits gained by modifying aspects of this program to improve adherence to effective strategies. Future model applications include addressing clinical scenarios for the effectiveness, cost-effectiveness, and value of information for *BRCA* carrier interventions that cannot yet be answered by clinical trials or observational studies.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.03.008.

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