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Cost-effectiveness of breast cancer screening policies using simulation

Y. Gocgun [a, *], D. Banjevic [b], S. Taghipour [c], N. Montgomery [b], B.J. Harvey [d], A.K.S. Jardine [b], A.B. Miller [d]

[a] Department of Industrial Engineering, Istanbul Kemerburgaz University, İstanbul Kemerburgaz Universitesi Muhendislik ve Mimarlik Fakultesi, Mahmutbey Yerleskesi Dilmenler Cad. No: 26, 34217 Istanbul, Turkey
[b] Centre for Maintenance Optimization and Reliability Engineering, University of Toronto, 40 St. George Street, Toronto, ON M5S 3G8, Canada
[c] Department of Mechanical and Industrial Engineering, Ryerson University, 350 Victoria Street, Toronto, ON M5B 2K3, Canada
[d] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, ON M5T 3M7, Canada

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ABSTRACT

In this paper, we study breast cancer screening policies using computer simulation. We developed a multi-state Markov model for breast cancer progression, considering both the screening and treatment stages of breast cancer. The parameters of our model were estimated through data from the Canadian National Breast Cancer Screening Study as well as data in the relevant literature. Using computer simulation, we evaluated various screening policies to study the impact of mammography screening for age-based subpopulations in Canada. We also performed sensitivity analysis to examine the impact of certain parameters on number of deaths and total costs. The analysis comparing screening policies reveals that a policy in which women belonging to the 40–49 age group are not screened, whereas those belonging to the 50–59 and 60–69 age groups are screened once every 5 years, outperforms others with respect to cost per life saved. Our analysis also indicates that increasing the screening frequencies for the 50–59 and 60–69 age groups decrease mortality, and that the average number of deaths generally decreases with an increase in screening frequency. We found that screening annually for all age groups is associated with the highest costs per life saved. Our analysis thus reveals that cost per life saved increases with an increase in screening frequency.

Introduction

Breast cancer is the most common cancer among women. It is estimated that in 2014, 24,400 Canadian women will develop breast cancer, and nearly 5000 of them will die from breast cancer [1]. There are certain risk factors affecting the development of breast cancer; examples include age, family history, breast density, and race. Breast cancer can be detected at early stages through mammography screening periodically applied to women through a screening program. Women diagnosed with cancer then receive treatment to cure the disease. Since mammography screening enables the detection of cancer at early stages, the resulting treatment may be more effective as compared to cancers presenting clinically, usually at later, more advanced stages.

Mammography screening is believed to lead to a reduction in breast cancer mortality by bringing forward the time of the diagnosis of cancer. It has been estimated that breast cancer mortality is reduced by 15% when mammography is applied [2]. Yet, there is controversy as to whether it should be applied to women belonging to certain age groups. This is mainly due to the fact that in some studies no effect of mammography screening was found, while mammography causes *overdiagnosis*, which is the diagnosis of cancers that would not otherwise present, leading to patient anxiety and unnecessary diagnostic procedures and treatment. Additionally, mammography leads to false-positive results, when the screening test suggests that an abnormality is present while cancer is actually absent.

Further, there is also controversy regarding the optimal screening policy that would specify the start age and end age of screening along with screening frequency. For example, the Canadian Task Force on Preventive Health Care recommends not routinely screening the 40–49 age group with mammography and recommends routinely screening the 50–69 age group every two to three years [3]. On the other hand, the American Cancer Society recommends annual mammography for women beginning at age 40 [4].

* Corresponding author. Tel.: +90 536 793 3600.
E-mail address: yasin.gocgun@kemerburgaz.edu.tr (Y. Gocgun).

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In this paper, we study the impact of mammography screening for age-based subpopulations in Canada. In particular, we address the question of which screening policy is the most cost-effective for the Canadian population. The study perspective of our work is the health system. Using a multi-state Markov model, we develop a breast cancer progression model, which includes both screening and treatment stages. We use computer simulation to evaluate various screening policies to determine optimal screening policy. We also perform sensitivity analysis on certain model parameters to identify which parameters have high impact on the output measures.

Literature review

There have been numerous studies on breast cancer screening [5–11]. While some studies have used computer simulation to measure the effect of screening policies, a large body of this research has focused on the U.S. population [12–16], with fewer conducted for the Canadian population [17–20]. We review the related literature below.

Humphrey et al. studied the effect of mammography screening on breast cancer in randomized, controlled trials [21]. They found that mammography led to a reduction in breast cancer mortality among women 40–74 years of age. Schousbe et al. studied the health benefits and cost-effectiveness of mammography [22]. Using a Markov microsimulation model, they evaluated various screening policies considering risk factors such as age, breast density, and family history of breast cancer. The result of their work indicates that mammography should be personalized on the basis of risk factors such as age and breast density. Hunter et al. developed a simulation model for breast cancer screening to evaluate the impact of including the 40–49 age group into the ongoing screening program in Ontario [17]. They estimated the total cost of screening and initial treatment for the case where age eligibility requirements change.

Okonkwo et al. studied the cost-effectiveness of breast cancer screening policies for India. They used a microsimulation model to estimate the cost of breast cancer screening, its effects on mortality, and its cost-effectiveness [23]. Their analysis focused on two modalities: physical breast examination and mammography screening. Ahern and Shen studied the cost-effectiveness of mammography and physical breast examination [24]. Using a microsimulation model, they compared screening policies recommended by a few major organizations against alternative policies. The results of their work indicate that alternative screening policies are more efficient.

Mandelblatt et al. studied the effects of mammography screening under different screening schedules [25]. They developed models of breast cancer incidence and mortality in the United States. The results of their work indicated that screening every other year maintained an average of 81% of the benefit of annual screening. In addition, they found that screening every other year from ages 50–69 years resulted in a median 16.5% reduction in breast cancer deaths as compared to no screening. Mandelblatt et al. modeled the impact of population screening on breast cancer mortality in the United States [26]. They used six simulation models to evaluate screening outcomes under varying strategies. The results of their study indicate that screening every other year from ages 50–74 years reduces the probability of breast cancer death. They also found that screening annually from ages 40–84 years lowers mortality, yet it yields more false-positives and over-diagnosed cases as compared to screening every other year. Hendrick and Helvie evaluated the recommendations of United States Preventive Services Task Force regarding mammography screening [27]. Using six Cancer Intervention and Surveillance Modeling Network models, they examined various screening policies. The results of their work suggest that annual screening of women 40–84 years old results in around 40% mortality reduction as compared to no screening.

In a recent study, Taghipour et al. evaluated breast cancer screening policies using simulation [18]. They developed a multi-state Markov model for cancer progression to evaluate the effect of mammography on women aged 40–59. Differing from our model, their model does not include cancer stages nor does it consider cancer progression after treatment.

Model description

Breast cancer progresses through stages and may be detectable in the preclinical stage through mammography screening. Women are screened periodically during a fixed period to detect breast cancer at an early stage. Screening detects cancers with a certain probability, which is called *sensitivity* of the screening test. If screening results are positive, then a woman will be referred to undergo diagnostic procedures. Further, a woman diagnosed with breast cancer will be referred to undergo treatment, which can be applied until the cancer is deemed to be in remission and then only reapplied if necessary (i.e., if the cancer recurs). The types of treatment used depend on various characteristics (eg, size, stage, and histology) of the cancer at initial diagnosis.

We model breast cancer progression using a multi-state Markov model. We chose this type of model because it was successfully used for modeling breast cancer progression [18,28–30] and it allows us to incorporate the effect of different states on output metrics. Our model consists of the following states:

H: *Healthy state*
0–3: Preclinical states
4: *Clinical state*
5: O*ther-cause death*
6: Death due to breast cancer

States 0–3 are preclinical (i.e., screen-detectable) states, which are primarily determined on the basis of tumor size. State 0 represents 'in-situ' cancer, with the other preclinical states being 'invasive' cancer states. State 4 indicates a breast cancer that presents clinically. We assume that cancer progresses sequentially through states 0–4 [17,23]. Further, state transition in our model occurs as follows. A woman in Healthy state can transition to any of the following states: State 0, Other-cause death, or continue to remain in the Healthy state. Transition from Healthy state to Other-cause death occurs when a woman dies of a cause other than breast cancer. A woman in any of States 0–2 can transition to the next preclinical state (e.g., from state 1–2), Other-cause death, or continue to remain in her current state. On the other hand, a woman in State 3 can transition to State 4 (clinically-evident cancer state), Other-cause death, or continue to remain in State 3. A woman in State 4 can transition to Death due to Breast Cancer, Other-cause death, or continue to remain in State 4. (see Fig. 1 for the schematic view of the progression model). Further, due to the Markovian property, the time each woman stays in a given state is assumed to follow an exponential distribution.

Note that the multi-state model depicted in Fig. 1 represents a natural progression of breast cancer, and therefore does not display how progression is affected when treatment is applied. More specifically, it does not describe how cancer progresses when it is detected through screening. We therefore provide the impact of detection of cancer through screening on cancer progression in Fig. 2, which shows that the diagnosis of a cancer can occur either

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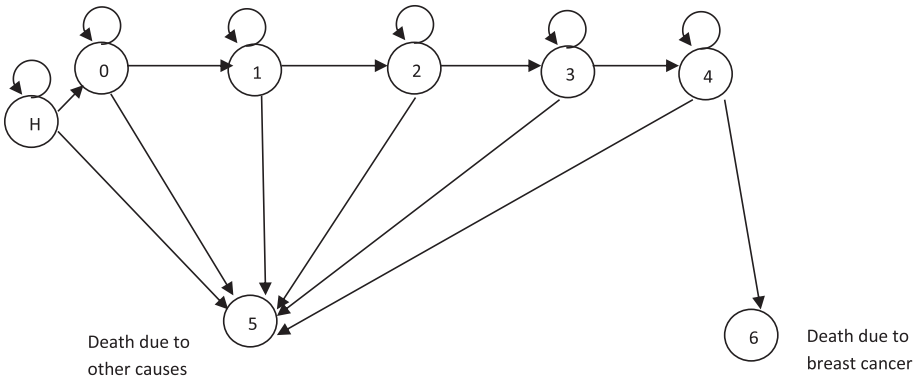

Fig. 1. A schematic view of the multi-state model for breast cancer progression. H denotes Healthy state; States 0–3 are preclinical (i.e., screen-detectable) states, and State 4 is a clinical state (i.e., clinically evident cancer). States 5 and 6 represent death due to causes other than breast cancer and death due to breast cancer, respectively.

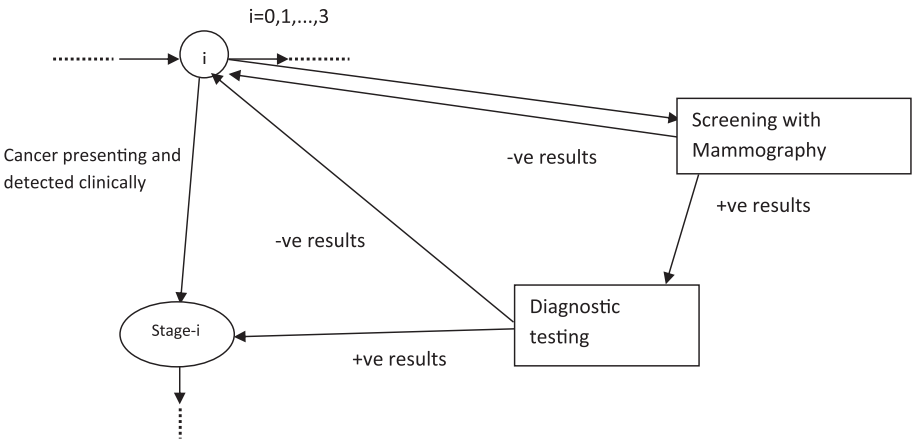

Fig. 2. The pathway for disease progression upon detection of cancer through clinical diagnosis or mammography screening followed by diagnostic tests.

clinically or through mammography screening. Note that a cancer diagnosed at State i is considered to be a stage-i cancer.

Fig. 3 provides a schematic view of the pathway for disease progression for stages 0, 1, 2, and 3 when treatment is performed. Note that we have the following additional states for the progression model with treatment: Post-treatment state (i.e., remission state), Local Recurrence, and Distant Recurrence. For women requiring treatment, cancer progresses as follows: women diagnosed and treated with Stage 0, 1, 2 or 3 can transition from those states to *local recurrence, distant recurrence,* death due to breast cancer, or death due to other causes; women with *local recurrence* can transition to *distant recurrence*, death due to breast cancer, or death due to other causes; women with *distant recurrence* (including those diagnosed with Stage 4 disease) will receive terminal care and transition to either death due to breast cancer or death due to other causes.

Parameter estimation and model validation

Parameter estimation

The parameters of the progression model need to be estimated using a rigorous procedure since the estimates of the parameters are populated into simulation as input parameters, thereby highly influencing simulation outputs. We therefore utilized one of the well-known estimation methods in Statistics, Maximum Likelihood Technique (MLT), for estimating crucial parameters of the model. To achieve this, we used data from the Canadian National Breast Cancer Screening Study (CNBSS). The CNBSS data contains extensive information for health records of women who underwent different modalities of screening between 1980 and 1989 in Canada, and belong to one of the age groups 40–49 and 50–59. The MLT utilizes the CNBSS data along with the assumption that sojourn times (i.e., time spent in a given state) follow an exponential distribution to compute the estimates of transition rates.

The parameters estimated by the MLT are state transition rates, which, as stated earlier, highly affect the outcome of simulation such as the number of screen-detected cancers and clinical cancers as well as the numbers of cancer deaths and deaths due to causes other than breast cancer. More specifically, we utilized the MLT technique for estimating transition rates of the treatment component of the model. Moreover, our estimates for transition rates are stage-based estimates, as the severity of cancer affects the rate of transition from, for example, local recurrence, to distant recurrence. Further, during the estimation procedure, we made certain assumptions owing to data scarcity. Namely, the number of women facing specific type of recurrence and possessing a particular stage is quite low. Hence, we combined the data for stages 2 and 3 (i.e., State 2 and State 3 cancers) assuming that the transition rates for these stages do not differ as they can both be viewed as advanced stages. Additionally, the estimation of the transition rates for Stage 4 was not performed through the MLT technique because very few cancers presented as this stage were found in the CNBSS database, which made it impossible to utilize the MLT technique. As for the

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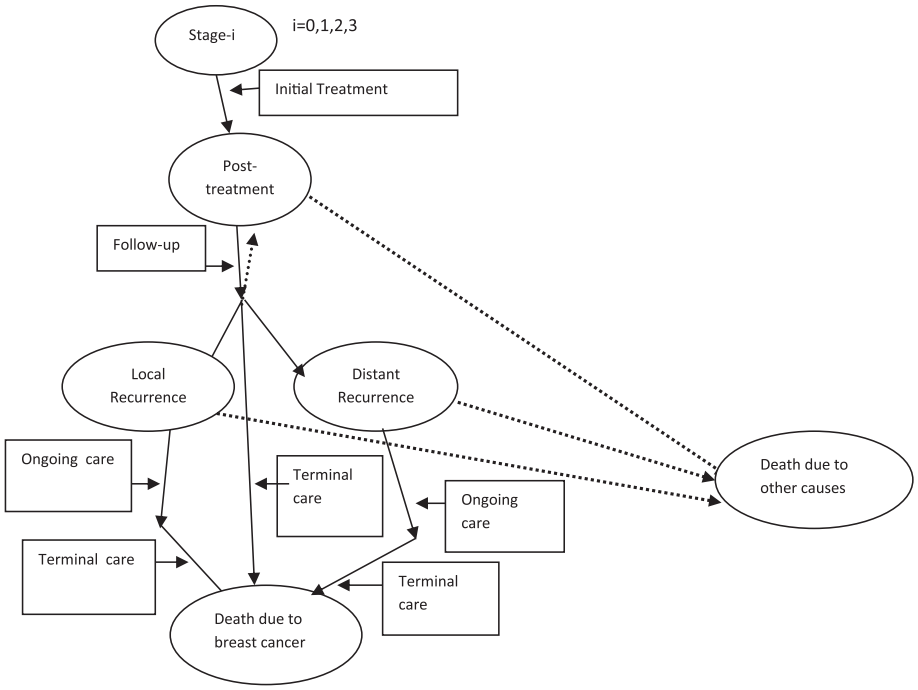

Fig. 3. A schematic view of the pathway of progression following treatment for breast cancer.

screening component of the model, which corresponds to the period between the beginning of cancer and the diagnosis of cancer, the estimates given in Taghipour et al. [28] were used.

Tables 1–3 present the estimates of the abovementioned transition rates for each combination of age group and stage.

Model validation

We validated our model through computer simulation using the estimates obtained by the MLT technique and the medical literature as well as being compared against the respective information extracted from the CNBSS data. Our validation consisted of two stages; the first stage deals with the validation of the screening component of the model whereas the second stage aims to validate the treatment component of the model. In the first stage of validation, the comparison was made considering the numbers of screen-detected cancers and clinically-detected cancers occurring during the CNBSS, with the second stage of validation focusing on the comparison of number of cancer deaths.

During validation, we populated a variety of input data obtained from the CNBSS data into simulation. Enrolment dates, number of screens, and follow-up period for each woman were computed using the database. Additionally, screening interval for each woman was approximated to be 1 owing to the fact that women were required to undergo screening annually in the trial. Additionally, recurrence and death info provided in the CNBSS data were used in the simulation.

The number of women who were simulated was 45,000; among them, nearly 25,000 and 20,000 women aged 40–49 and 50–59

Table 1
The estimates of state transition rates for in-situ (Stage-0) cancer for the 40–49 and 50–59 age groups. Local rec. and distant rec. correspond to local recurrence and distant recurrence, respectively.

	Local rec.	Distant rec.	Cancer death
Age-group: 40–49			
Remission	0.028	0	0
Local Rec.	–	0	0
Distant Rec.	–	–	0
Age-group: 50–59			
Remission	0.25	0	0
Local Rec.	–	0	0.071
Distant Rec.	–	–	0

Table 2
The estimates of state transition rates for stages 1, 2, 3, and 4 for age group 40–49.

	Local rec.	Distant rec.	Cancer death
Stage 1			
Remission	0.01	1.6×10^{-5}	–
Local Rec.	–	0.062	0.013
Distant Rec.	–	–	0.555
Stages 2&3			
Remission	0.018	0.024	–
Local Rec.	–	0.165	–
Distant Rec.	–	–	0.386
Stage 4			
Remission	–	1	–
Local Rec.	–	–	–
Distant Rec.	–	–	0.386

Table 3
The estimates of state transition rates for stages 1, 2, 3, and 4 for age group 50–59.

	Local rec.	Distant rec.	Cancer death
Stage 1			
Remission	0.009	2.5×10^{-5}	–
Local Rec.	–	0.052	–
Distant Rec.	–	–	0.137
Stages 2&3			
Remission	0.016	0.105	–
Local Rec.	–	0.13	–
Distant Rec.	–	–	0.423
Stage 4			
Remission	–	1	–
Local Rec.	–	–	–
Distant Rec.	–	–	0.423

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Table 4
The estimates of screening-related parameters for the 40–49, 50–59, and 60–69 age groups.

Screening-related parameters	Estimated values	Source
Age group distribution for 40–49, 50–59, and 60–69 age groups	(0.349, 0.372, 0.279)	Statistics Canada
Screening sensitivity for 40–49, 50–59, and 60–69 age groups	(0.608; 0.745; 0.82)	Taghipour et al. [28]
Proportion of prevalent cancer at the beginning of screening for 40–49, 50–59, and 60–69 age groups	(0.0011, 0.0022, 0.0023)	Canadian Cancer Statistics, 2013 [29]
Screening participation rate	0.73	Breast Cancer Control in Canada, 2012 [31]
Specificity	0.95	Personal communication
Stage distribution	*Screen-detected cancers:* **For 40–49 age group:** (0.1;0.59;0.27;0.04;0) **For 50–59 age group:** (0.1;0.6;0.3;0;0) **For 60–69 age group:** assumed to be the same as the 50–59 age group *Clinically-detected cancers:* **For 40–49 age group:** (0,0.39,0.53,0.08,0) **For 50–59 age group:** (0,0.36,0.56,0.07,0) **For 60–69 age group:** assumed to be the same as the 50–59 age group	The CNBSS data
Overdiagnosis probability	0.20 for screen-detected cancers 0.35 for prevalent cancers	Personal communication
Compliance rate	1	Personal communication
Distribution for diagnostic procedures	Non-invasive work-up: 81.2% Invasive work-up- Needle Biopsy: 15.5% Excisional work-up (excisional biopsy): 3.5%	Organized Breast Cancer Screening Programs in Canada, 2013 [32]

years, respectively. We first simulated the cancer progression of each individual using attributes, such as number of screens, enrolment dates, etc. This implies that, during simulation, each woman is scheduled to undergo screening at a predetermined time, and that simulation ends when any of the following events occur: the end of the designated follow-up period, the diagnosis of cancer, or death of woman due to breast cancer or causes other than breast cancer. To deal with the stochasticity of transition times and time of death, the number of replications was set to 50. Then, in the second stage of validation, we simulated the progression of cancer after diagnosis for women diagnosed with cancer, by using the actual number of screen-detected and clinically-presenting cancers. This resulted in about 500 women beingsimulated in the second stage.

The results of the validation process revealed that the results of the simulation is consistent with the CNBSS results [5,6] that reported 14-year follow-up. These comparisons, however, revealed that the rates affecting death for the 40–49 age group were underestimated by the simulation. However, further simulations indicated that these differing death rates do not affect the results of the health economic comparison of screening policies. As a result, we did not further adjust the simulation parameters affecting the death rates for women aged 40–49 years.

Numerical experiments

Input data

The input data populated into the simulation model are given in Tables 4–7. Cancers detected at the first screens are called *prevalent cancers* and are included in our model. Some women have non-progressive cancers *overdiagnosed* by screening. These are breast cancers that would not have otherwise been detected. The *specificity* of mammography screening is the probability that the test will be negative in women who do not have breast cancer. Finally, we have used the term *compliance rate* to represent the percentage of women who are diagnosed with cancer and accept treatment.

We consider three age groups: 40–49, 50–59, and 60–69 years. Screening sensitivity values were obtained from the medical literature, while the proportion of prevalent cancers, screening participation rate, stage distribution, distribution for diagnostic procedures were obtained from various sources on the web (see Table 4 for the sources on the web). Specificity, overdiagnosis, and compliance rate were obtained through personal communication from Dr Nicole Mittman (Sunnybrook Hospital in Toronto). Participation rate and stage distribution of screen-detected cancers were assumed to be the same for each age group. Due to a lack of data, we assumed the stage distribution of clinically-presenting cancers for the 60–69 age group is the same as that for the 50–59 age group. The estimates of cost parameters were acquired from Sunnybrook Research Centre in Toronto as well as the medical literature. Because the estimates obtained from the medical literature were older data, we converted those estimates into present value using an inflation calculator available on the web [1]. For cost of chemotherapy and cost of hormone therapy, it was assumed that the corresponding estimates for the 60–69 age group are the same as those for the 50–59 age group. Whereas the cost estimates are assumed not to differ by age group for the other cost parameters.

The stage-based distributions of treatment procedures were obtained from the recent literature (see Table 6). According to the data, a patient can undergo either breast conserving surgery or mastectomy. Additionally, the distribution of radiotherapy depends on whether the patient underwent breast conserving surgery or not. Further, the distribution of the duration of diagnostic procedures (for follow-up testing) were obtained from the medical literature.

The estimates for transition rates such as healthy to preclinical state, preclinical to clinical state, and other-cause death states were obtained from Taghipour et al. [28] whereas estimates such as transition rate from local recurrence state to distant recurrence state and remission state to distant recurrence state were obtained through the use of the CNBSS data.

Experimental design

We simulate 10,000 women and set the number of replications to 100 to obtain suitably precise results considering the 95%

[1] Inflation calculator: http://www.bankofcanada.ca/rates/related/inflation-calculator/.

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Table 5
The estimates of cost parameters for each cancer stage along with their sources.

Cost parameters	Estimated values ($)	Reference year	Source
Cost for mammography screening (the cost includes mammography and radiology)	183 **In today's dollars:**[a] 185	2012	Ontario Health Insurance Plan
Cost for diagnostic tests (non-invasive work-up; the cost includes mammography, radiology, physician clinic visit)	445.9 **In today's dollars:** 451	2012	Ontario Health Insurance Plan
Cost for diagnostic tests (invasive work-up- Needle Biopsy (the cost includes physician clinic visit, needle biopsy procedure and pathology)	745.5 **In today's dollars:** 754.1	2012	Sunnybrook Research Centre, Toronto, ON
Cost for diagnostic tests (Excisional work-up; the cost includes physician clinic visits, excision, pathology)	1,652.4 **In today's dollars:** 1,671.4	2012	Sunnybrook Research Centre, Toronto, ON
Cost for Radiotherapy	5,014 **In today's dollars:** 5,071	2012	Ontario Health Insurance Plan
Cost for breast conserving surgery	4,937 **In today's dollars:** 4,993	2012	Ontario Case Cost Initiative
Cost for mastectomy	6,956 **In today's dollars:** 7,036	2012	Ontario Case Cost Initiative
Cost for chemotherapy for stages 0–4	(382; 382; 2,419; 4,091; 2,650) for the 40–49 age group **In today's dollars:**[b](545;545;3,450;5,835;3,780) (116; 116; 446;1,529;1,139) for the 50–59 age group **In today's dollars:** (165;165;636;2,181;1,625)	1995	Will et al. [33]
Cost for hormone therapy for stages 0–4	**40–49 age group**: (123; 123; 331;136; 1,349) **In today's dollars:** (175; 175;472;194;1,924) **50–59 age group**: (267; 267; 897; 624; 1,801) **In today's dollars:** (381;381;1,279;890;2,569)	1995	Will et al. [33]
Cost for initial treatment for stages 0–4	(8,238; 8,238; 9,089; 9,052; 9;538) (total cost) (for a 3-month period) **In today's dollars:** (11,751; 11,751; 12,965;12,912;13,605)	1995	Will et al. [33]
Cost for follow-up for stages 0–4	(2,313;2,313; 1841; 1429,-) (total cost) (for a 5-year period) **In today's dollars:** (3,299;3,299;2,626;2038,-)	1995	Will et al. [33]
Cost for ongoing care for stages 0–4	(506;506;442;535;1,455) (monthly cost) **In today's dollars:** (722;722;630;763;2,075)	1995	Will et al. [33]
Cost for terminal care for stages 0–4	(4,905;4,905;7,177; 11,849;14,169) (total cost) (for a 3-month period) **In today's dollars:** (6,997;6,997;10,237;16,902;20211)	1995	Will et al. [33]

[a] Inflation calculator: http://www.bankofcanada.ca/rates/related/inflation-calculator/.
[b] Inflation calculator: http://www.bankofcanada.ca/rates/related/inflation-calculator/.

Table 6
The distribution of treatment procedures for each cancer stage.

Treatment procedures	Stages				
	Stage-0	**Stage-1**	**Stage-2**	**Stage-3**	**Stage-4**
Breast conserving surgery	66	65	47	15	18
Mastectomy	25	31	49	66	18
Radiation therapy[a]	38; 55[a]	59;88	64;89	77;76	46;0
Chemotherapy	0	14	58	71	43
Hormone therapy	22	63	65	67	51

[a] Radiation therapy used after breast conserving surgery (valid for each stage).

Table 7
Durations of diagnostic and treatment procedures along with their sources.

Duration for procedures	Estimated values	Source
Duration for diagnostic tests	nearly 1.5 months	Breast Cancer Control in Canada, 2012 [31]
Duration for initial treatment	3–6 months	Will et al. [33]
Duration for terminal care	3 months	Will et al. [33]

confidence level. In line with the related literature [23,24], the discount factor (D.F.) was set to 0.97, and was applied only to costs. The discount rate (D.R.) is therefore equal to 3.1% since it is obtained through the following formula: D.F = 1/(1 + D.R.). Each woman is followed 20 years. Hence, the time horizon over which costs are evaluated was set to 20 years. The screening period was set to 10 or 20 years. In particular, screening periods for the 40–49 and 50–59 age group were set to 20 whereas the screening period for the 60–69 age group was set to only 10 as screening is not advised for older women. Screening policies are determined by screening intervals for each age group. For example, the policy (3,2,2) requires that women aged 40–49 years be screened once in 3 years, while women in the other age groups be screened once every other year. (The description of other policies are given in Table 8.) In line with the recent literature [18], maximum screening interval for each age group was set to 5. Further, women exceeding the age of 69 years in the screening program are assumed to have the same transition rates as those belonging to the 60–69 age group.

We evaluated the effect of various screening policies on the total number of deaths due to breast cancer and total costs, which

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Table 8
The description of screening policies for age groups 40–49, 50–59, and 60–69.

Screening policy	Description
(-,5,5)	The 40–49 age group: Not screened; The 50–59 and 60–69 age groups: Screened once every 5 years
(-,3,3)	The 40–49 age group: Not screened; The 50–59 and 60–69 age groups: Screened once every 3 years
(-,2,2)	The 40–49 age group: Not screened; The 50–59 and 60–69 age groups: Screened once every other year
(-,1,1)	The 40–49 age group: Not screened; The 50–59 and 60–69 age groups: Screened each year
(5,5,5)	The 40–49 age group: Screened once every 5 years; The 50–59 and 60–69 age groups: Screened once every 5 years
(5,3,3)	The 40–49 age group: Screened once every 5 years; The 50–59 and 60–69 age groups: Screened once every 3 years
(5,2,2)	The 40–49 age group: Screened once every 5 years; The 50–59 and 60–69 age groups: Screened once every other year
(5,1,1)	The 40–49 age group: Screened once every 5 years; The 50–59 and 60–69 age groups: Screened each year
(3,5,5)	The 40–49 age group: Screened once every 3 years; The 50–59 and 60–69 age groups: Screened once every 5 years
(3,3,3)	The 40–49 age group: Screened once every 3 years; The 50–59 and 60–69 age groups: Screened once every 3 years
(3,1,1)	The 40–49 age group: Screened once every 3 years; The 50–59 and 60–69 age groups: Screened every year
(1,5,5)	The 40–49 age group: Screened every year; The 50–59 and 60–69 age groups: Screened once every 5 years
(1,3,3)	The 40–49 age group: Screened every year; The 50–59 and 60–69 age groups: Screened once every 3 years
(1,2,2)	The 40–49 age group: Screened every year; The 50–59 and 60–69 age groups: Screened once every other year
(1,1,1)	The 40–49 age group: Screened every year; The 50–59 and 60–69 age groups: Screened every year

includes screening, diagnostic, and treatment costs. Examples of other output measures include cost per life saved, number of women screened to avert one death, and cost per life saved. Among them, we included cost per life saved and number of women screened to avert one death in our computational analysis.

Note that cost per life saved for a given policy depends on total cost and number of deaths. Since most of the cost data is obtained using the related literature, and the data affecting number of deaths mainly came from CNBSS results, we emphasize that costs per life saved partially depend on CNBSS results. Regarding the effect of CNBSS results, it should also be noted that the comparison of cost per life saved values rather than individual values of cost per life saved is considered in identifying the best screening policy.

Results

Results of the simulations are presented in Table 9. For each policy, Table 9 provides average total cost (screening, diagnostic, and treatment costs), average mortality (i.e., average number of deaths), average cost per life saved (i.e., average incremental cost per death averted compared to "no screening") over 100 replications, and average number of women screened to avert one death. Cost per life saved for a given policy was computed by dividing the difference between the costs of that policy and the 'no-screening' policy by the difference between the average mortalities for these two policies. On the other hand, number of women screened to avert one death for a given policy is computed by dividing 10,000 by the difference between average number of deaths obtained by the 'no-screening' policy and that obtained by the respective policy. Standard errors for total cost and mortality values are around 80,000 and 1, respectively. This implies that any two cost values are significantly different from each other if one exceeds the other by at least $320,000 at the 95% confidence level. In addition, the difference between two mortality values must be at least 4 in order to conclude that they are statistically different at the 95% confidence level.

The results reveal that mortality decreases with an increase in screening frequency. Average mortality takes the smallest value when women belonging to each age group are screened annually. When cost per life saved (l.s.) is considered an output measure, the policy (-,5,5) turns out to be the optimal policy, yielding nearly $537,000/l.s. This indicates that, in order for a policy to be cost-effective, mammography should not be applied to women belonging to the 40–49 group. According to the cost per l.s. criterion, the policies (-,3,3) and (-,2,2) can be considered to be efficient policies since the average cost/l.s. for them are reasonably close to that for the optimal policy.

Further, our results yield the following observations. First, increasing the screening frequency from every 5 years to every 3 or annually for the 40–49 age group while keeping the remaining ones unchanged does not significantly decrease mortality. Second, increasing the screening frequencies for those aged 50–59 and 60–69 years decreases mortality, but increasing the frequency of re-screening reduces cost-effectiveness. Third, in terms of cost per

Table 9
Results for the comparison of screening policies.

Screening policy	Average total cost($)	Average number of deaths	Incremental cost per death averted compared to "no screening" ($)	# of women screened to avert one death
No-screening	11,589,915	107.4	–	
(-,5,5)	14,980,971	101.1	537,410	1585
(-,3,3)	16,298,486	99.9	626,973	1332
(-,2,2)	18,414,393	97.0	654,940	960
(-,1,1)	24,091,226	94.7	981,265	785
(5,5,5)	17,013,442	100.5	781,488	1441
(5,3,3)	18,271,716	97.3	662,220	991
(5,2,2)	20,487,643	94.3	678,181	762
(5,1,1)	26,216,094	90.9	884,826	605
(3,5,5)	17,576,151	99.2	728,253	1217
(3,3,3)	19,199,313	96.8	717,868	943
(3,2,2)	21,492,492	96.5	906,000	915
(3,1,1)	27,060,465	92.0	1,001,979	648
(1,5,5)	19,536,517	99.9	1,055,326	1328
(1,3,3)	21,460,563	96.5	903,906	916
(1,2,2)	24,509,554	95.1	1,051,232	814
(1,1,1)	32,145,000	88.9	1,109,886	540

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Table 10
Parameters and their ranges used for sensitivity analysis.

Parameter	Value range
Participation rate	75% and 125% of base-case (b.c.) values
Mammography sensitivity	75% and 125% of b.c. values
Treatment costs	75% and 125% of b.c. values
Transition rate from distant recurrence to cancer death	50% and 150% of b.c. values
Transition rate from local recurrence to distant recurrence	50% and 150% of b.c. values
Transition rate from healthy state to preclinical state	50% and 150% of b.c. values

Table 11
Results of sensitivity analysis for average number of deaths.

Parameters	Average number of deaths			
	Low value	Base-case value	High value	Difference
Participation rate	103.8	101.1	100.8	−3.0
Mammography sensitivity	102.5	101.1	99.9	−2.6
Treatment cost	101.1	101.1	101.1	0.0
Transition rate from distant recurrence to death	81.1	101.1	109.4	**28.3**
Transition rate from local rec. to distant rec.	97.4	101.1	103.4	6.0
Transition rate from healthy state to preclinical state	51.8	101.1	152.2	**100.4**

life saved, the policies in which the screening interval for the 40–49 is 5 or (−) outperform those in which the corresponding interval is 3 or 1. Fourth, the average number of deaths generally decreases with an increase in screening frequency. Finally, screening annually is not cost-effective (i.e., it results in a relatively high cost per life saved value).

Sensitivity analysis

To investigate the impact of certain parameters on the output metrics, we performed one-way sensitivity analysis in which the values of individual parameters were changed one at a time and the output metrics for the '-,5,5' policy, the optimal policy for the base-case scenario on the basis of cost/l.s., were calculated by simulation as before. We varied participation rate, mammography sensitivity, treatment costs, and the estimates of certain transition rates. The levels of these parameters are given in Table 10. Note that discount rate was not changed in sensitivity analysis. The results of our sensitivity analysis are presented in Tables 11 and 12. For a given performance metric, 'low value' ('high value') in these tables corresponds to the value of the performance metric obtained by setting the value of the respective parameter to 75% or 50% (125% or 150%) of the corresponding base-case value. The results of sensitivity analysis for average number of deaths reveal that the transition rate from distant recurrence state to cancer death and transition rate from healthy state to preclinical state have high impact on number of deaths. Whereas the sensitivity results for average total cost reveals that participation rate, treatment cost, and transition rate from healthy state to preclinical state have high impact on total cost (the 'difference' values corresponding to the effective parameters are bolded in Tables 11 and 12).

Table 12
Results of sensitivity analysis for average total cost.

Parameters	Average total cost			
	Low value	Base-case value	High value	Difference
Participation rate	14,261,411	14,980,970	15,758,000	**1,496,589**
Mammography sensitivity	14,975,575	14,980,971	15,006,310	30,734
Treatment cost	12,869,936	14,980,970	17,092,006	**4,222,069**
Transition rate from distant recurrence to death	14,805,324	14,980,971	15,052,911	247,587
Transition rate from local rec. to distant rec.	15,094,036	14,980,970	14,898,744	−195,292
Transition rate from healthy state to preclinical state	9,218,258	14,980,971	20,742,572	**11,524,313**

Discussion

Our findings for women aged 40–49 years are compatible with the findings from the Canadian National Breast Screening Study (CNBSS), but those for women aged 50–59 years are not and women aged 60–69 years were not included in the CNBSS. This is because we included assumptions in our simulation derived from the results of other breast screening trials that were not confirmed by the long-term follow-up of the CNBSS. Further, our finding that screening women aged 50–69 years every 5 years is cost-effective is dependent on an assumption of effectiveness that has so far not been verified in any study. It is likely therefore that many may wish to delay implementing policies based upon our simulation until the assumptions built into our simulation have been verified. This is compatible with the suggestions by others that further research on the effectiveness of breast screening is required.

Our finding that cost per life saved increases with an increase in screeening frequency indicates that, only some policies in terms of cost per life saved are cost-effective to the Canadian government. For a given value of cost threshold, the government can identify the most cost-effective policy through the results of our policy analysis.

It is worth pointing out that this work is an economic analysis of breast cancer screening policies for the Canadian population. Because of differences in technology and quality of performance of that technology, there may be significant variations of screening effectiveness world-wide.

Our work has certain limitations. We considered only average-risk women thereby ignoring risk factors other than age in deriving parameter estimates. Due to the complexity of breast cancer progression, we did not include transitions between cancer stages; rather we assumed that the cancer stage of a woman is known with a certain distribution upon the detection of cancer. Further, due to data scarcity, we assumed that the estimates for certain age groups are generally the same as those for other age groups for which estimation procedure is complete owing to having sufficient data.

Conclusions

We studied breast cancer screening for age-based subpopulations in Canada. Using a multi-state model, we developed a breast cancer progression model that includes both screening and treatment stages. We tested screening policies using computer simulation, with the view of assessing the impact of mammography screening on well-studied output measures.

Our findings are summarized below.

- The screening policy, not screening women aged 40–49 years while screening women aged 50–69 years every 5 years (-,5,5) is the best policy with respect to cost per life saved. This implies that, according to this performance metric, women aged 40–49 years should not be screened.

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- Increasing the screening frequencies for women aged 50–59 and 60–69 years decrease mortality, but with decrease of cost-effectiveness.
- The average number of deaths generally decreases with increased screening frequency.
- Screening annually is not cost-effective.
- The transition rate from distant recurrence state to cancer death and transition rate from healthy state to preclinical state have a high impact on the estimated number of deaths.
- Participation rate, treatment cost, and transition rate from healthy state to preclinical state have a high impact on the estimated total costs.

Conflict of interest statement

The authors declare no conflict of interest.

Ethical approval

The authors read and complied with the policy of the journal on ethical consent. The approval for the standards of animal was not required.

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