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Simulation modeling of change to breast cancer detection age eligibility recommendations in Ontario, 2002–2021

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Abstract

Purpose: The purpose of this project was to demonstrate the development and use of a decision support tool based on simulation modeling of breast cancer screening to evaluate the implications for the provision of health services and the economic impact of extending routine radiographic screening for breast cancer to women in the 40–49 age group between 2002 and 2021.
Methods: The main method was computer simulation with a Markov model that used published estimates of population size by age group, breast cancer prevalence and incidence, screening program participation rate, sensitivity and specificity of the screening test and diagnostic test, stage transition probabilities, directed diagnosis rates and costs.
Findings: The model predicted that changes to age eligibility requirements would result in the detection of an additional 6610 women with breast cancer in Ontario requiring treatment, at an additional cost of CAN$ 795 per case. These costs include those related to screening, diagnosis and initial treatment and apply to the 20-year period.
Conclusions: The model provided a useful decision support tool for those planning and implementing breast cancer screening programs.

Keywords: Computer simulation; Mass screening; Breast neoplasms; Markov modeling

1. Introduction

Breast cancer represents a significant threat to the health of Canadian women. Almost 1 in 10 will develop the disease and 1 in 26 will die of it [1]. In 2002, there were 20,500 new cases of breast cancer diagnosed in Canada and 5400 deaths, a mortality rate, which exceeds the Organization for Economic Cooperation and Development (OECD) countries median [2]. Ontario has one of the world's highest incidences of breast cancer; which increased by 17% between 1971 and 1996. Despite this, breast cancer mortality decreased by 9% between 1986 and 1996, likely due to both improved treatments and earlier detection through screening. The 5-year survival rate after diagnosis now exceeds 80% [3].

According to the National Population Health Survey, 62% of Ontario women in 1996 aged 50–69 reported having had a mammogram within two years, a larger proportion than in other provinces [3]. In 2000–2001, about 70% of the province's women in the 50–69 age group received a mammogram. A national survey determined that three-quarters of the women underwent the procedure as a result of a regular checkup or a recommendation for routine screening. The systematic collection of data by the Ontario Breast Screening Program allows insight into the results of screening. For example, in 1998 the program provided initial and repeat screening to 98,594 women. This represents a participation rate of 16% for women in the 50–69 age group. These procedures resulted in the diagnosis of 623 breast cancers [4].

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Published literature suggests mammograms reduce the number of deaths from breast cancer [5–7], although there are studies, which have suggested a contrary position [8,9]. A meta-analysis carried out on trials of screening found a statistically significant reduction in mortality in women who had initiated screening in their 40s. The mortality reduction was 18% (relative risk = 0.82, 95% CIs = 0.71–0.95) in women followed an average of 13 years [6]. Previously published meta-analyses of the trials with only 7–9 years of follow-up did not show any significant mortality benefit in this age group. However, concerns remain about the higher rates of false positive diagnoses of breast cancer in younger women, the lower sensitivity of mammography in this age group, and the appropriateness of recommending widespread screening in this population given the lower incidence of breast cancer. Current recommendations on mammographic screening reflect this uncertainty. For example, the American Cancer Society [10] and the US Preventive Services Task Force [11] both recommend screening from age 40, while the Canadian Cancer Society [12] and the Canadian Task Force on Preventive Health Care [13] recommend starting at age 50. The recommendations on the frequency of screening (e.g. annual or biennial) from these groups also vary [14].

It has been suggested by some stakeholder groups, such as the Canadian Association of Radiologists, that radiographic screening could be justified for women in the 40–49 age group [15]. From 1992 to 1996, the number of new cases of breast cancer in Ontario women aged 45–49 was similar to the number found for women aged 50–54 and exceeded the number diagnosed within the 55–59 age group [3]. Currently, Ontario is one of four provinces that do not admit women below age 50 to their organized screening programs. A move toward screening women aged 40–49 would have both implications for the provision of services and their related costs, that need to be fully explored by decision makers.

While the study of breast cancer is characterized by a large volume of research, it also clearly evinces controversy [16]. This lack of a consensus is particularly difficult for decision makers committed to formulating evidence-based policy. Furthermore, policy makers are sometimes faced with pressure from advocacy groups to implement new programs on the basis of little evidence. One approach to resolving this decision making dilemma is to provide policy makers with a method, such as computer simulation to model the impacts of screening, that rapidly incorporates the results of new and possibly contradictory studies into the policy formation process. Any decision making process can be challenged on the basis of the data it uses. A simulation model that permits rapid alteration of input data would allow policy makers to model expeditiously a range of possible outcomes.

Many published simulation models of breast cancer detection programs are based on cancer classification systems that incorporate different levels of cancer development [17–20]. Each of these models requires starting values for each cancer category, e.g. the number (or proportion) of people in each cancer category must be known before a simulation can proceed. These stage-wise proportions are usually unknown, although sometimes they are derived from clinical observations [19,20]. For example, Boer et al. relied on the distribution of observed cancers when estimating the distribution of undetected cancers in the pre-screened population [20].

Specifically, they assumed that only 4.6% of undetected cancers were in situ, 1.5% were grade T1a, 6.3% were T1b, 32.6% were T1c, and 55% were grade T2 or more severe. While these proportions match the distribution of observed cancers, it is unlikely that they matched the true distribution of breast cancers in the unscreened population, because early-stage cancers persist asymptomatically and therefore are under-represented in clinical incidence databases [21].

The simulation model in this paper differs from other simulation models in that the initial starting values are based on the consensus views of experts who believe that the early stages of breast cancer span longer time periods compared to later stages. An in situ carcinoma might persist for many years before promoting to a Stage I cancer, if ever, while Stage III cancers are believed to proceed to Stage IV in a matter of months. Therefore, at any point in time, the prevalence of in situ cancers in the unscreened population must far exceed the prevalence of Stage IV cancers, in spite of the dominance of later-stage cases observed in clinical settings [21,22]. In the current model, the starting values for underlying prevalence were estimated from the reported incidence of cancer (by stage) corrected for the average duration of each stage.

The purpose of this project is to demonstrate the development and use of a decision support tool based on simulation modeling of breast screening. The simulation model will be used to evaluate the impact on the provision of health services and on the economic impact of extending routine radiographic screening for breast cancer to women in the 40–49 age group.

2. Material and methods

This section describes the three main steps used in this study: (1) developing a theoretical model of the breast cancer detection in Ontario; (2) identifying the data for input into the simulation model; and (3) running the simulation model.

2.1. Theoretical model of breast cancer detection

The theoretical model of breast cancer screening detection was based on three main assumptions: (1) an established screening program in Ontario detects breast cancers in many women each year; (2) many breast cancers are detected outside of the established program (referred to as ‘‘directed diagnosis’’); and (3) cancers will progress through stages over time. The model simulates a population of individuals as they progress through the stages of breast cancer and as they move through the health care system. It is

assumed that women are promoted from each stage to the next stage based on estimates of stage transition probabilities rates (analogous to state transition probabilities in Markov models). Stages were defined according to the TMN classification of malignant tumors developed by the American Joint Committee on Cancer [23,24]. For the purposes of the theoretical model, it was assumed that cancer cases move through stages in a predictable order; healthy women might develop Stage 0 (in situ) cancers, which will then progress in sequence through Stages I–IV. In this model, breast cancer also includes ductal carcinoma, not elsewhere specified (Fig. 1).

There are a number of ways that cases of breast cancer can be detected outside of established breast cancer screening programs. For example, a diagnosis of breast cancer could result from presentation of symptoms, familial history, or advice from a physician to seek screening outside of a formal program when a patient reaches a certain age. These are referred to in this paper as ''directed diagnosis'' unless an examination was motivated by a positive result from the breast cancer screening program. The flows through health care services are illustrated in Fig. 2.

The results of a screening test may be either positive or negative. The relative proportion of positive and negative screening test results is dependent on the prevalence of undetected cancers in the population and on the accuracy of the screening test. Cases with positive screening test results move to a diagnostic sample for confirmation; cases with negative results are returned to the general population.

The general population of women consists of six groups: those without breast cancer, and those with undetected cancers at Stages 0–IV. Consequently, there are five different health services groups in the population: negative screening test, positive screening test, negative diagnostic test, positive diagnostic test, and those undergoing initial treatment, i.e.

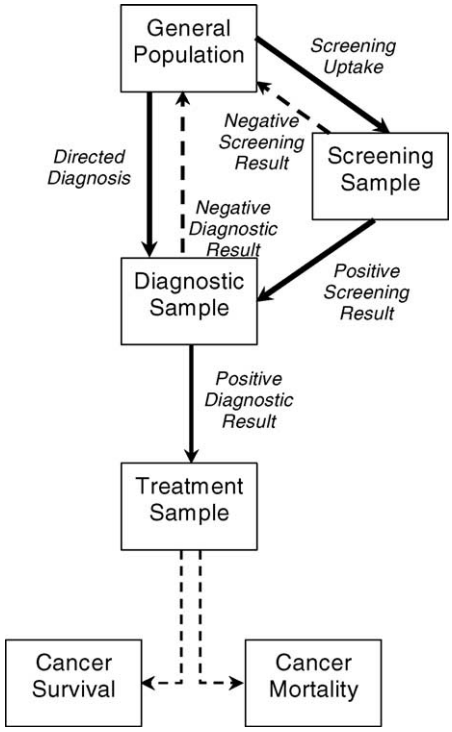

Fig. 2. Patient flows through health services with an established screening program.

any combination of: surgical excision (open, partial mastectomy, complete mastectomy), adjuvant chemotherapy, hormone therapy and/or radiotherapy.

2.2. Sources and values for input into the simulation model

The main method was a computer simulation with a Markov model. Several different types of input data were

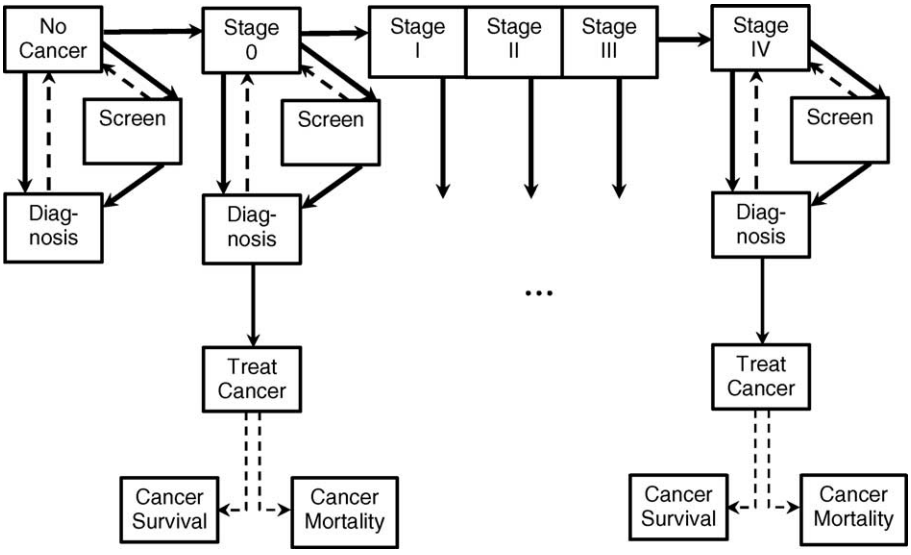

Fig. 1. Theoretical model of breast cancer screening (note that the columns for Stages I–III are not depicted, but are identical to Stage 0). Each vertical arrow represent the probability that an individual in state *X* will move to state *Y* within a 1-year period. The arrows in the top row of the conceptual model represent the *annual stage transition probabilities*, which are an example of transition probabilities seen in Markov models.

Table 1
Input values used to populate the simulation model

	Age group											
	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Population												
2001	452,866	522,745	505,137	444,339	397,860	305,558	251,752	226,398	210,300	185,244	121,077	107,580
2006	449,000	483,800	541,000	509,400	442,600	395,000	302,200	244,000	211,400	186,300	149,600	129,500
2011	458,600	479,100	501,700	544,600	506,700	439,000	389,300	292,600	228,400	188,200	152,000	163,200
2016	486,600	488,700	497,100	505,600	541,600	502,200	432,500	376,300	274,400	204,600	155,100	185,200
2021	515,800	516,700	506,600	501,100	503,200	536,700	494,500	418,400	353,200	246,800	170,300	202,300
Incidence (# cases per year)												
Stage 0	11	41	105	162	178	146	119	129	119	94	54	34
Stage I	26	82	168	255	341	319	325	358	361	336	201	144
Stage II	48	121	196	266	282	245	219	213	211	208	139	132
Stage III	10	25	40	53	56	46	41	39	37	43	31	39
Stage IV	5	10	18	24	33	30	34	32	33	33	25	28
Prevalence (per 100,000)												
Stage 0	78	184.1	343.4	491.9	650	756.3	877.8	1014.3	1088.9	11811	1151.2	1108.3
Stage I	181.6	396.4	671.6	1184.1	1447	1636.6	1827.5	1983	2123.1	2407.7	2819.5	2819.5
Stage II	36.4	76.4	128.1	277.5	352.1	394	458.5	484.8	519.8	621.4	695.9	898.4
Stage III	4	7.9	13.5	23	31.1	35.3	43.7	45.5	49.7	59	67.6	88.3
Stage IV	1.1	1.9	3.6	5.5	8.4	10	13.7	14	15.8	17.8	20.6	25.7
Participation rate (%)	0	0	10	10	8.8	10.1	10.8	10.1	7.8	0	0	0
Sensitivity (%)												
Stage 0	76	76	76	74	74	74	74	74	74	74	74	74
Stage I	88	88	88	87	87	87	87	87	87	87	87	87
Stage II	94	94	94	94	94	94	94	94	94	94	94	94
Stage III	97	97	97	97	97	97	97	97	97	97	97	97
Stage IV	99	99	99	99	99	99	99	99	99	99	99	99
Specificity (%)	91	91	91	91	91	91	91	91	91	91	91	91
Stage transition (%)												
Stages none–0	0.065	0.065	0.065	0.246	0.246	0.246	0.246	0.246	0.246	0.246	0.246	0.246
Stages 0–I	25.9	25.9	25.9	29.9	29.9	29.9	29.9	29.9	29.9	29.9	29.9	29.9
Stages I–II	7.9	7.9	7.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9
Stages II–III	12.8	12.8	12.8	8	8	8	8	8	8	8	8	8
Stages III–IV	62.5	62.5	62.5	49.6	49.6	49.6	49.6	49.6	49.6	49.6	49.6	49.6

used in the simulation model. These were: population estimates, the incidence and prevalence of breast cancer, screening uptake rates, breast cancer stage transition probabilities, test performance characteristics (sensitivity and specificity of the screening and diagnostic tests), directed diagnosis rates and information on costs. Each input data type is described in more detail below.

Population estimates for women, by 5-year age intervals, in the province of Ontario were obtained from the 2001 Census of Canada [25]. Population projections for the years 2003, 2011, 2016 and 2021 were obtained from the Ontario Ministry of Finance [26]. Age-specific incidence rates for breast cancer were derived by applying age-stage-specific estimates from the National Cancer Institute SEER Cancer incidence public-use database 1973–1997, to the overall incidence rates obtained from the Ontario Cancer Registry for breast cancer in the years 1992–1997 [27,28]. The screening program participation rate, by age group, was calculated on data obtained from the Ontario Breast Screening Program [29]. The compliance rate (follow-up after positive screen results) was taken to be 98%.

The sensitivity of mammography was assumed to be 60% for women aged 40–74 years and to be 87% for women aged 50–74 years [30]. The specificity of the screening test in the Ontario Breast Screening Program ranged from 87 to 93% [29]. The sensitivity and specificity of the diagnostic tests varied depending on the type of test (i.e. fine needle aspiration, cytologic diagnosis of breast fibroadenoma, fine needle biopsy, fine needle aspiration, guided fine needle aspiration cytology or image guided large core needle biopsy) [29–36]. For this study, sensitivity was taken to be 88% and specificity was 96% for fine needle aspiration biopsy. While nurse examination is part of the Ontario Breast Screening Program, the sensitivity and specificity of the physical examination was not considered separately because any manually detected lump would likely be confirmed by mammography.

No published, actual estimates on stage transition probabilities from one cancer stage to the next were found, although it is generally believed that younger women pass through the stages more quickly than older women. In order to estimate average stage transition probabilities, simulations were undertaken using a wide range of clinically plausible growth-rates and the impact on simulation outcome observed. The approach used was similar to a published approach used to determine stage to stage transition probabilities for colorectal cancer [37]. The rates included in the two scenarios generate simulations with cancer rates that are stable from year to year and consistent with the annual incidence rates in Ontario.

No published estimates on directed diagnosis rates, that is, the probability that a woman with undiagnosed breast cancer (at a given stage) would seek diagnosis (within the next 12 months) outside of the established Ontario Breast Screening Program, were identified. Given that it is probable that the likelihood of directed diagnosis would increase with stage, the rates were assumed to be 5% per year for women with Stage 0 or Stage I breast cancer, while for women with more advanced cancers, the rates were assumed to be 20, 44, and 70% for Stages II, III, and IV cancers, respectively.

Cost data were taken from a number of sources. The costs, in Canadian dollars, of screening were assumed to be $82.30 per screen [38]. The total cost of directed diagnosis was taken to be $76.50. This estimate was based on the assumption that a directed diagnosis requires a visit to a physician who then initiates a referral to a radiology facility. The least expensive family physician visit is coded AOO1 at $17.30. The standard screen is a bilateral mammogram done on dedicated equipment that carries a code X185. It includes two fees for the technical and professional components of the process and is valued at $59.20 [39]. Costs for initial treatment by stage, were taken from the published literature [40], expressed in 1995 Canadian dollars. Costs and the number of screens, treatments, and diagnoses were discounted over the 20-year period using 3% as the annual discount rate [41].

The values used to populate the simulation model are shown in Table 1. All default values were entered into Microsoft Excel 2000 spreadsheets that are linked with a software tool, *iThink* [42].

3. Results

Table 2 shows the results of the simulation modeling for Ontario women in 2002. The model predicted that 137,549 women aged 50 and over would be screened, that 190,097 women would require diagnostic tests; and that these tests

Table 2
Projected number of screening and diagnostic tests and initial treatments, and related costs for women with breast cancer, Ontario, 2002

	Number	Unit cost ($)	Cost ($)
Aged 50+			
Screening tests	137,549	82.3	11,320,219
Diagnostic tests	190,097	76.5	14,542,506
Detected cancers	8,250		
Treated			
Stage 0	1,402	8,238	11,542,966
Stage I	3,508	8,238	28,900,588
Stage II	2,447	9,089	22,237,733
Stage III	488	9,052	4,428,941
Stage IV	405	9,538	3,861,930
Total cost			96,834,883
Age 40+			
Screening tests	236,140	82.3	19,434,219
Diagnostic tests	198,698	76.5	15,200,423
Detected cancers	9,152		
Treated			
Stage 0	1,617	8,238	13,312,564
Stage I	4,065	8,238	33,483,474
Stage II	2,566	9,089	23,315,325
Stage III	497	9,052	4,505,390
Stage IV	407	9,538	3,877,314
Total costs			113,128,709

Note costs for Stage 0 cancers assumed to be the same as for Stage I.

Table 3
Comparison of projected number of tests and related costs between Scenario 1 (screening those over the age of 50 years) and Scenario 2 (screening those over the age of 40 years), discounted using 3% annual discount rate

	Number			Costs ($)		
	50+ years	40+ years	Difference	50+ years	40+ years	Difference
Screening tests	2,724,837	4,333,454	1,608,616	224,253,853	356,642,860	132,389,007
Diagnostic tests	3,354,258	3,498,328	144,070	256,600,426	267,621,803	11,021,377
Initial treatments	138,469	145,079	6,610	1,193,100,203	1,244,926,239	51,826,036
Cost per case				12,089	12,884	795
Total				1,673,954,482	1,869,190,902	195,236,420

would result in 8250 cancers detected that would require treatment for all stages (Stage 0 = 1402; Stage I = 3508; Stage II = 2447; Stage III = 488; Stage IV = 405). The costs related to these tests were: $11.3 million for screening, $14.5 million for diagnoses, and $71.0 million for treatment, resulting in a total of $96.8 million for screening, diagnosis and initial treatment of breast cancer in women aged 50 and over in Ontario in 2002. For women aged 40–74 the model predicted that 236,140 women would be screened, that 198,698 women would require diagnostic tests; and that 9152 cancers would be detected that would require treatment for all stages (Stage 0 = 1617; Stage I = 4065; Stage II = 2566; Stage III = 497; Stage IV = 407). The 2002 costs related to these tests include $19.4 million for screening, $15.2 million for diagnostic tests, $78.5 million for treatment reflecting a total of $113.1 million for screening, diagnosis and initial treatment of breast cancer in women aged 40 and over in Ontario in 2002.

A comparison of the projections based on screening those over the age of 50 with those over the age of 40 shows that an extra 6610 cancers would be detected, costing an additional $51.8 million or an additional $795 per case between the years 2001 and 2021 (Table 3). The 20-year trend in the projected number of screening tests, diagnostic tests and detected cancers requiring treatment for women over age 40 and over age 50 are shown in Fig. 3. The number of screening and diagnostic tests rises steadily in both age groups, while the trend in the number of cancers detected appears relatively stable. The trend in total cost per case

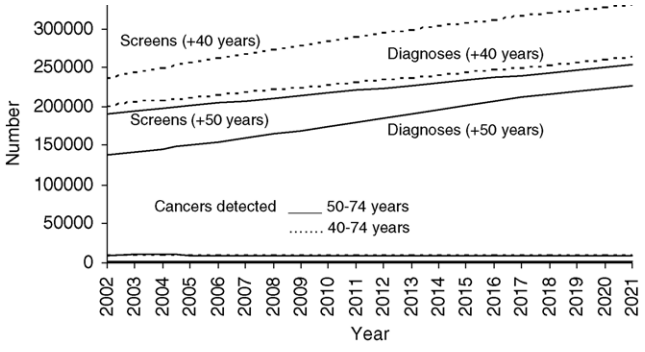

Fig. 3. Projected number of screening and diagnostic tests and initial treatments for women with breast cancer, aged 50 years and over and aged 40 and over, Ontario, 2002–2021.

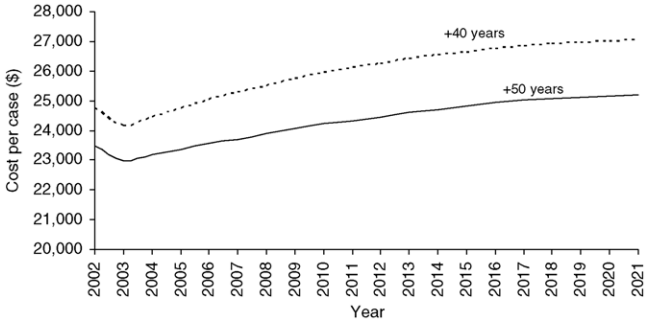

Fig. 4. Projected total costs of screening and diagnostic tests and initial treatments for women with breast cancer, aged 50 years and over and aged 40 and over, Ontario, 2002–2021.

based on screening, diagnosing and treating breast cancer in Ontario over the 20-year study period is shown in Fig. 4. The cost per case dips between 2002 and 2003 before gradually rising and leveling out over the remaining 18 years.

4. Discussion

This study has demonstrated the utility of computer simulations to model the impact of two different screening scenarios (women over the age of 50 versus women over the age of 40) on the provision of screening tests, diagnostic tests, initial treatments, and related costs for breast cancer in Ontario from 2002 to 2021. If the age eligibility recommendations were modified to include women between the ages of 40 and 49 years, the Ontario health system would require a total of 5.8 million screening tests, 4.6 million diagnostic tests, and would detect 188,886 cancers, over the 20-year period. Provision of these services was projected to cost $2.5 billion. Modifying the age eligibility requirements from the current recommendations for women over the age of 50 years, to include women between the ages of 40 and 49 years, would result in the detection of an additional 6610 women with breast cancer, costing an additional $795 per case.

The limitations of this study ought to be considered before any conclusions are drawn. There are three main limitations associated with modeling exercises. First, the accuracy of the results is dependent on the validity of the

model's assumptions. For example, in the current model it was assumed that a Stage IV cancer would pass through each stage from 0 to III; that is, growing malignancies do not skip stages. For example, in the current model it was assumed that an untreated cancer would predictably pass through each stage from 0 to IV; that is malignancies do not skip stages or stop at any stage, although both can happen. In terms of the simulation modeling, it was impossible to derive estimates from the literature that would allow us to incorporate the heterogeneity of the breast cancer growth.

Second, the accuracy of the results is dependent on the precision of the data used to populate the model. For example, no estimates of transit time (the length of time a tumor remains in a given stage) were identified in the published literature. Consequently, it was necessary to compute these times mathematically, using the best available information. Finally, all models that attempt to estimate long-term outcomes are at risk of failing to account for significant future events that fundamentally alter the phenomenon being modeled. In the present case, it is entirely possible that new and more accurate screening tests and more effective treatments will be introduced for breast cancer that would make current projections inaccurate. However, the risks of technological change radically altering projections in the model are less likely in the short-term, so that estimates for the near term may be viewed with considerable confidence.

The results simulated by this model were the number of screening tests, diagnostic tests, initial treatments and their related costs. It is important to emphasize that the ultimate outcome of screening programs is the decrease in morbidity and mortality related to breast cancer. It was beyond the limits of this project to consider this issue, although it would theoretically be possible, for example, to consider the impact of screening on overall life expectancy.

The computer simulations were based on what were considered to be the most reasonable input data. The strength of the simulation model that accompanies this report is that policy makers can use the software to model different scenarios. For example, the Ministry of Health and Long-term Care may consider a scenario with no organized screening at all. We tested an extreme modeling scenario with no organized screening program and found that while savings of an estimated $2270 per detected case would be realized, the lack of organized screening would result in the failure to identify 27,660 cases requiring treatment.

Using default input values in our model, it was predicted that extending formal screening to women in their 40s would result in a 4.2% (n = 7620) increase in the number of cancers detected from 2002 to 2021 in this age group at an added cost of $173 million for screening, $14.3 million for diagnosis and $58.8 million for initial treatment (in constant 2002 Canadian dollars). From a policy perspective, the value of this screening yield must be assessed by considering what advantage is known to result from earlier detection. That is, women in their 40s with cancers detected by mammography would become eligible for screening at 50 under present guidelines and high-risk younger patients would normally receive directed diagnosis regardless of age. The immediate policy question is, what clinical value, e.g. longevity or quality of life, results from the earlier detection of the 7620 cancers? The further challenge to policy makers is balancing the answer to the preceding question against the additional cost of earlier detection. As is so often the case, the policy issue becomes one of cost-effectiveness and opportunity costs in an era of constrained resources.

Finally, one must consider the equity implications in a system of publicly-funded health care of postponing the detection of cancers known to exist in a defined population simply on the basis of age eligibility criteria for screening. Age has been suggested as a clinically legitimate criterion upon which services such as cardiac surgery might be allocated. However, it is unclear if the evidence supports a similar position with reference to breast screening.

The aim of this study was to illustrate the use of a computer simulation model to predict the system impacts of extending the age-eligibility requirements for organized breast cancer screening from the current scenario (+50 years) to include women in the 40–49 year age group. Based on the most reasonable evidence-based input assumptions, the model predicted that these changes would result in the detection of an additional 6610 women in Ontario requiring treatment for breast cancer, at an additional cost of $795 per detected case.

Acknowledgements

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