Cost-effectiveness of combining MRI with mammography for breast cancer screening among high-risk population in Ottawa

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ABSTRACT

Background: Based on previous research, conventional mammography screening has been found to be ineffective for women at high risk, mainly because high-risk women have high breast density and a fast progression rate of breast cancer. Recently, MRI screening was proposed as an additional complementary screening for high-risk women in Ottawa. The addition of MRI to mammography to screen the high-risk population is worth exploring as it may well address the limitations of mammography, especially since MRI has higher sensitivity.

Purpose: The goal of this study is to assess the cost-effectiveness off adding MRI to mammography screening for early detection among women of the high-risk population in Ottawa by using conventional values for the society's/government's willingness to pay for one life year gained (US$ 50,000).

Methods: A discrete-event simulation model was developed to evaluate the cost-effectiveness of adding MRI screening to mammography for high risk women breast screening in Ottawa. Three risk groups were considered; BRCA1, BRCA2 and other high risk. Based on breast annual incidence, screening features, breast cancer progression among high-risk women, treatment and breast cancer survival rates, the model simulates a hypothetical cohort consisting of 5000 women progressing from age 30 to 100 (or to natural death) and calculates the accumulated life years and costs in order to predict the cost of one life year gained by each screening strategy. Univariate sensitivity analysis was performed on the key parameters to determine the robustness of the simulation outcomes. Paired t-tests were used to determine whether the parameters' variations are statistically significant or not.

Results: In the base-case scenario, the incremental cost-effectiveness ratio (ICER) of mammography compared to both screening was CAN$30,043.48 /life year gained (95%CI ±2524.40) which means the addition of MRI to mammography is a cost-effective intervention according to the commonly used willingness-to-pay threshold of US$50,000 per life-year gained. The findings of the sensitivity analysis indicate that the cost-effectiveness of adding MRI screening is statistically significant for most of the parameter variations,

however, the degree of change in the ICER is not hugely impactful as in all cases the ICER remained well below the commonly used willingness-to-pay threshold per life year gained.

Conclusion: Study results suggested that the addition of MRI has an important role in improving high risk women screening in terms of increasing life years gained compared to receiving mammography screening only. The results of this study support the recommendations of Cancer Care Ontario and the Ontario Health Technology Advisory Committee guidelines of expanding the Ontario Screening Program to integrate MRI with mammography screening for high risk women aged 30 to 69 years.

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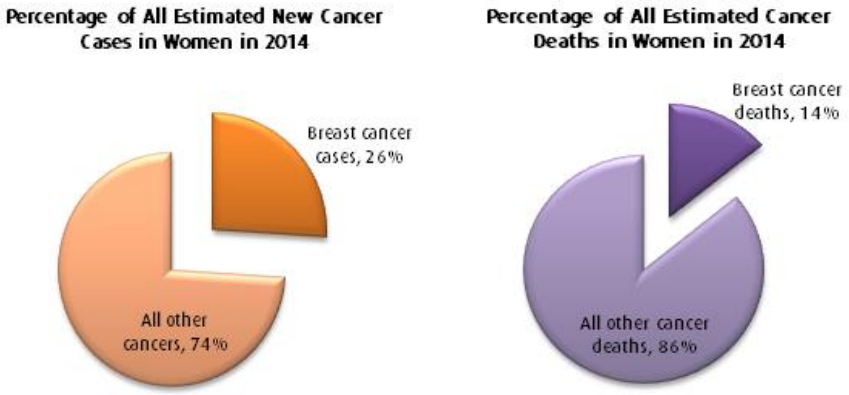
1. BACKGROUND

1.1 Breast Cancer in Canada

Breast cancer continues to be the most common type of cancer among women in Canada and currently comprises 26% of new cases of cancer within this demographic group (Figure 1). Based on 2007 estimates of the probability of developing and dying from breast cancer, one out of nine Canadian women is anticipated to develop this disease over the course of her life (i.e., by age 90) and, sadly, one out of 29 will eventually die as a result. In 2014, 24,400 Canadian women were expected to have breast cancer, of which 9,500 cases were expected to occur in Ontario. Furthermore, breast cancer ranks second after lung cancer as the most common cause of cancer fatality in women, a level that represents 14% of overall cancer fatalities among women, of which 1,950 deaths were estimated to occur in Ontario (Figure 1) (Canadian Cancer Society, 2014; Statistics Canada, 2011).

Figure 1: Estimated Breast Cancer Incidence and Deaths among Canadian Women for 2014



Source: Canadian Cancer Society, 2014

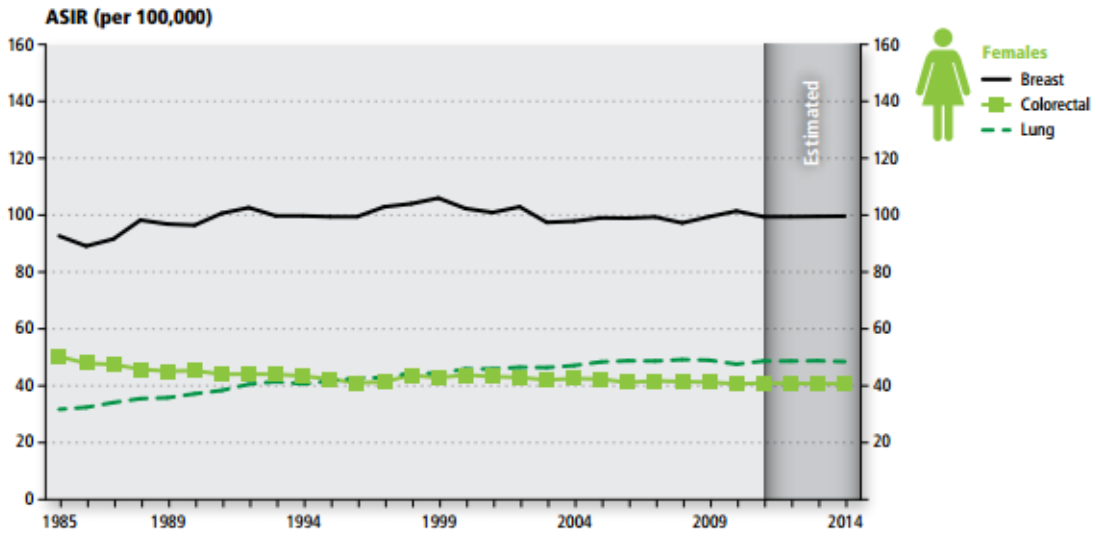
1.2 Increase in Breast Cancer Incidence Contrasted with Decrease in Mortality Rates

According to the Canadian Cancer Statistics 2014 report which was published by the Canadian Cancer Society, the rates of breast cancer incidence increased

during the early part of the 1990s (Figure 2). The incidence escalated largely as a result of opportunistic screening through mammography prior to 1988 which was the beginning of the organized provincial breast screening program. Since that year, the rates have varied. The explanation for this variation is not clear, though it is likely associated with the continued use of mammography and long-term alterations in hormonal factors, including an earlier age of menarche, breastfeeding, a later age of menopause, the use of oral contraceptives and a later age of full-term pregnancy. Around 2002, the breast-cancer incidence decreased, perhaps as a result of the reduction in the usage of hormone replacement therapy (HRT) among post-menopausal women.

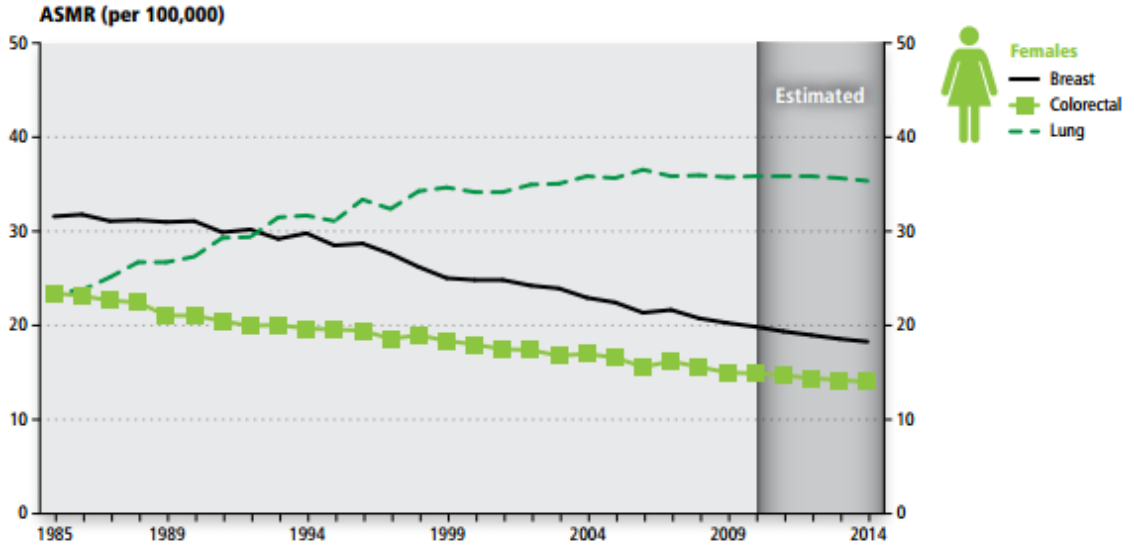
On the other hand, the mortality rate due to breast cancer has decreased by almost 43% since 1986 (Figure 3) (Medical Advisory Secretariat, 2010; Canadian Cancer Society, 2014).

Figure 2: Age-standardized Incidence Rates (ASIRs) for Selected* Cancers, Females, Canada, 1985-2014



Source: Canadian Cancer Society, 2014

Figure 3: Age-standardized Mortality Rates (ASMRs) for Selected* Cancers, Females, Canada, 1985–2014



Source: Canadian Cancer Society, 2014

Furthermore, according to recent Canadian cancer statistics, women who developed breast cancer have an 88% chance of surviving for more than five years (Canadian Cancer Society, 2013). Data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER)[1] indicate that this rate increases up to 100% if the cancer is detected at Stage 0 or I and decreases to 20% if the cancer is not detected until Stage IV (as explained below under "Factors Affecting Breast Cancer Progression and Treatment"). In addition, the five-year relative survival rates for stages II and III were 86% and 57% respectively (Gloekler Ries & Eisner, n.d.).

Regular and effective screening leading to early detection combined with treatment improvements may be the main factors underlying the decline in breast cancer

[1] SEER is the abbreviation of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. This organization generates and disseminates cancer statistics in an effort to reduce the burden of cancer among the U.S. population (National Cancer Institute, n.d.b).

mortality and the increase in survival rates (Medical Advisory Secretariat, 2010; Canadian Cancer Society, 2014).

1.3 Breast Cancer among Women with Elevated Risk

Within the larger population, there is a cohort of women who are classified as having a high risk of developing breast cancer. There are many factors that may contribute to increasing the probability of developing breast cancer including the women's age (as the risk of developing breast cancer increases with age), breast density (as higher levels of breast density are associated with a higher risk of developing breast cancer), Ashkenazi Jewish ancestry and hormone replacement therapy (HRT). Nevertheless, the most important risk factors that are considered by the majority of organized breast screening programs to determine high-risk women are any of the following: 1) A genetic mutation known as Breast Cancer Antigen 1 or 2 (BRCA1/2). These are human genes that generate tumour suppressor proteins. The role of these proteins in repairing damaged DNA ensures that they help to stabilize the cell's genetic material. The mutation or alteration of either of these genes to the extent that its protein product is not made or does not operate properly means that damage to the DNA might not be fully repaired. Consequently, there is a higher probability that cells will acquire additional genetic alterations that can develop into cancer (National Cancer Institute, n.d.a). These genetic mutations can be identified through genetic testing. 2) A child, parent or other close relative who has been identified as having this genetic anomaly. 3) A family history of breast cancer and a greater than 25% lifetime probability of at some point developing breast cancer as can be confirmed through a genetic assessment. 4) The experience of having received radiation therapy to her chest before reaching age 30 as part of a treatment program for another cancer or condition (e.g., Hodgkin's disease) (Ministry of Health and Long-Term Care, 2009; Afonso, 2009; Canadian Cancer Society, n.d.).

1.3.1 Lifetime Risk of High-risk Women

Members of this high-risk group of women have a two to five times higher risk of developing breast cancer during their lifetime than other women. Usually breast cancer develops at a younger age (20 years earlier on average) among high-risk women than within the general population and the disease is more aggressive with a faster rate of progression (Ministry of Health and Long-Term Care, 2008). Moreover, breast cancer is the main cause of cancer mortality among Canadian women falling within the age range of 30 to 39 years (Canadian Cancer Society, 2012; Statistics Canada, 2011).

Lifetime risk percentages for women with a family history but no proven genetic mutation usually are estimated based on several well-developed models such as those of Claus, Gail, Tyrer-Cuzick (IBIS) and BRCAPRO (Ahern, 2008). For those with genetic mutations, one research study indicated that the lifetime risk of developing breast cancer among women with the BRCA1 genetic mutation is 85% and among those with the BRCA2 genetic mutation is 70%. Another study concluded that the lifetime risk ranges between 25% and 50% among women with the BRCA1 or BRCA2 genetic mutation while the lifetime risk ranges between 11.5% and 25% among other high-risk women. For comparison, the lifetime risk is 9% among members of the rest of the population. Of the total number of breast cancer incidences, between 5% and 10% are linked to BRCA1 or BRCA2 mutations (Dunfield & Severn, 2007).

1.4 Factors Affecting Breast Cancer Progression and Treatment

Breast cancer prognosis, treatment options and survival depend on the following:

1. The stage of cancer which classifies cancers based on the tumour size and on whether it is located in the breast only or has metastasized to the lymph nodes or to other organs in the body. One of the best methods to describe the stage of

breast cancer is the TNM classification which stands for "Tumour, Nodes and Metastases" (Table 1) (Canadian Breast Cancer Foundation, n.d.; National Cancer Institute, n.d.c).

Table 1: TNM Stage Grouping

Stage 0	Tis	N_0	M_0
Stage I	T_{1*}	N_0	M_0
Stage IIA	T_0	N_1	M_0
	T_{1*}	N_1	M_0
	T_2	N_0	M_0
Stage IIB	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIIA	T_0	N_2	M_0
	T_{1*}	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1, N_2	M_0
Stage IIIB	T_4	N_0, N_1, N_2	M_0
Stage IIIC	Any T	N_3	M_0
Stage IV	Any T	Any N	M_1

Note: * T_1 includes T_1mic.

T - Primary Tumour

T0. No evidence of primary tumour

Tis. Carcinoma in situ

T1. Tumour 2 cm or less in greatest dimension

T2. Tumour more than 2 cm but not more than 5 cm in greatest dimension

T3. Tumour more than 5 cm in greatest dimension

T4. Tumour of any size with direct extension to the chest wall or to skin only

N - Regional Lymph Nodes

N0. No regional lymph node metastasis

N1. Metastasis in movable ipsilateral axillary lymph node(s)

N2. Metastasis in fixed ipsilateral axillary lymph node(s) or in clinically apparent* ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis

N3. Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement; or in clinically apparent*ipsilateral internal mammary lymph node(s) in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymphnode(s) with or without axillary or internal mammary lymph node involvement

M - Distant Metastasis

M0. No distant metastasis

M1. Distant metastasis (TMN Classification Help, 2005)

2. The breast cancer type such as: Ductal Carcinoma In-Situ (DCIS), Lobular Carcinoma (LC), Infiltrating Ductal Carcinoma (IDC) and so on. (National Cancer Institute, n.d.c)

3. Estrogen receptor (ER) and progesterone receptor (PR) status in the tumour tissue. Some breast-cancer cells have receptors that are able to receive estrogen and progesterone hormone molecules in the manner of a lock and key. The presence of these receptors (positive) means that the hormones will stimulate the growth of the cancer (Canadian Breast Cancer Foundation, n.d.; National Cancer Institute, n.d.c).

4. Human epidermal growth factor type 2 receptor (HER2/neu) levels in the tumour tissue. If the levels of HER2/neu genes or HER2/neu protein are higher than normal, then the cancer has a higher probability of growing more rapidly and of spreading elsewhere in the body (Canadian Breast Cancer Foundation, n.d.; National Cancer Institute, n.d.c).

5. The question of whether the tumour tissue is triple-negative (that is, cells that lack receptors for estrogen, receptors for progesterone or high levels of HER2/neu). These tumours behave more aggressively and are more difficult to treat while having a high rate of recurrence (Canadian Breast Cancer Foundation, n.d.; Canadian Cancer Society, n.d.).

6. Progression rate of the tumour. The faster the rate of progression of the tumour, the greater the probability that there will be lymph node involvement and hence a longer treatment plan and a slightly lower rate of survival. The rate of progression is higher among genetic mutation carriers and more specifically among BRCA1 women (National Cancer Institute, n.d.c).

7. Recurrence rate of the breast cancer tumour (National Cancer Institute, n.d.c)

8. History of breast cancer (i.e., having had breast cancer in the past) (National Cancer Institute, n.d.c)

9. A woman's age, overall health and whether she continues to have menstrual periods (National Cancer Institute, n.d.c)

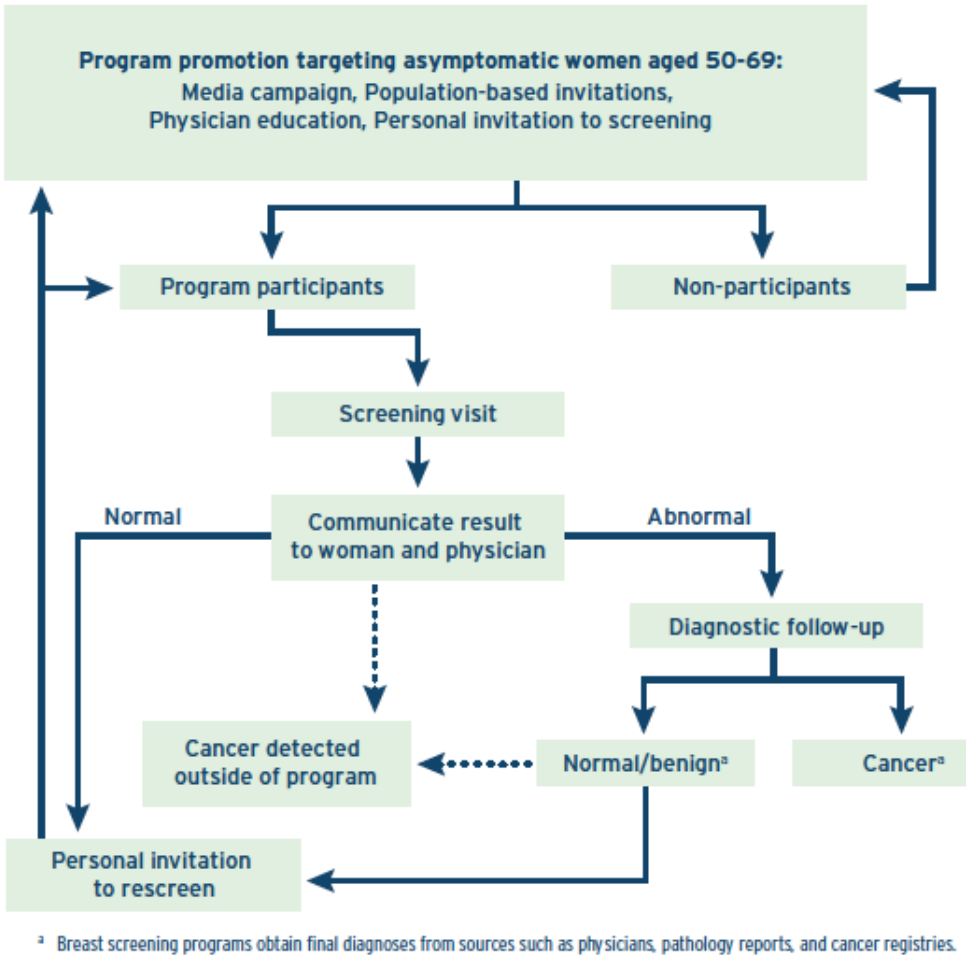
1.5 Organized Breast Cancer Screening Programs

While the treatments for breast cancer have improved, a lot of effort has been invested in prevention. The first organized breast-cancer screening program in Canada was launched in 1988 in British Columbia with all the other provinces and territories following suit. The Canadian federal government introduced the first stage of the Canadian Breast Cancer Initiative (CBCI) in December 1992. Over a five-year period this program delivered $25 million and incorporated among its top goals the Canadian Breast Cancer Screening Initiative (CBCSI). Funding on the federal level has been extended for the CBCSI, first by means of Health Canada and currently by means of the Public Health Agency of Canada (Public Health Agency of Canada, 2006).

Initially all breast-cancer screening programs offered biennial two-view, bilateral mammography for women aged 50 to 69 at average risk of developing breast cancer and without a history of cancer. In addition, some programs extend to

women who do not fall within this age range and some also offer testing at higher frequencies based on multiple factors such as genetic mutations or other risk factors (as described above in this report). Finally, some programs also include survivors of breast cancer (Public Health Agency of Canada, 2006). See Figure 4 for the typical pathway used in the screening program.

Figure 4: Pathway of a Breast Cancer Screening Program



Source: Public Health Agency of Canada, 2006

1.6 Breast Cancer Screening for High-risk Women

Many preventive options are available for women at high risk of developing breast cancer. One of the most frequently recommended options is prophylactic

mastectomy, which is a surgical procedure to remove one or both breasts, generally referred to as risk-reducing mastectomy (RRM). The objective of this procedure is to prevent or at least drastically decrease the probability of breast tumours among women who have a greatly elevated probability of developing them. Currently, available data suggest that this form of surgery could lead to a greater than 90% decrease in the likelihood of moderate- and high-risk women developing this disease (National Cancer Institute, 2006).

On the other hand, RRM may have a profoundly negative psychological impact as a result of the associated elimination of ordinary breast functions and the alteration in body image (National Cancer Institute, 2006). One of the other preventive options that is frequently prescribed for genetic mutation carriers is Tamoxifen. Tamoxifen is "a selective estrogen receptor modulator that has an inhibitory effect on estrogen receptors in breast tissue and a proliferative effect in the endometrium" (Bougie & Weberpals, 2011). According to a study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), Tamoxifen reduced the risk of developing breast cancer among BRCA2 women by 62% but did not reduce the risk of developing breast cancer among BRCA1 women (Bougie & Weberpals, 2011). Moreover, the use of Tamoxifen can lead to side effects including an elevated risk of strokes, an elevated risk of blood clots (particularly in the legs and lungs), uterine and endometrial cancers, bone loss among premenopausal women, cataracts, depression, mood swings and loss of libido (National Cancer Institute, n.d.d). Given the side effects of the previously mentioned preventive options, an alternative is necessary and the best alternative is effective breast screening.

1.6.1 Mammography Screening

The conventional breast-screening strategy used for women aged 50 years or over who are at average risk of developing breast cancer is mammography (Ministry of Health and Long-Term Care, 2009).

Mammography screening is a process of examining breast tissues by using low-energy x-ray radiation without using any contrast agents. The breast should be compressed during mammography examination to obtain a clear image of the tissues. The period of examination is usually between 15 and 20 minutes.

Recently digital mammography (DM) screening has replaced film-mammography (FM) where the image is obtained directly without film from an x-ray-sensitive solid-state receptor (Enriquez & Linitsky, 2009). This development has increased the sensitivity (ability of detecting cancer when it truly exists) of mammography, particularly among women younger than 50 (DM= 49%; FM=35%), among premenopausal women (DM=47%; FM= 38%) and among women with high breast density (DM= 38%; FM= 36%) (Moore et al., 2009; Pisano et al., 2005).

1.6.1.1 Mammography Drawbacks

Given the fact that screening is more effective when it is able to detect the tumour before the invasive phase or at an early stage when the tumour's diameter is smaller than or equal to 10 mm and when the systemic recurrence rate falls below 10% (Kurian et al., 2004; Issacs et al., 2004; Lehman et al., 2004), mammography is not an ideal screening strategy for younger women mainly due to a higher level of breast density among these women, and this may lead to higher false-negative rate because of the low sensitivity among these women. Although it is reasonably effective in women over 50, 2% of these women will die of breast cancer despite mammography screening in the general population. In a very high-risk population, because of the faster rate of progression of breast cancer among these women, the sensitivity for detecting very early stage disease has to be much higher (and the case

fatality rate lower) for the overall mortality rate to be acceptable (Dos Santos Silva, 1999; CancerLink, n.d.).

The findings of studies that evaluate the effectiveness of mammography screening among women at high risk of developing breast cancer have been very dissatisfying (Warner et al., 2012). For example, based on the findings of two prospective studies (Scheuer et al., 2002; Vasen et al., 2005), one retrospective study and one series that incorporated prospective and retrospective data (Brekelmans et al., 2001), at the time of detection the dimensions of 40% to 78% of invasive cancers[2] were larger than 1 cm, 20% to 56% had lymph-node involvement, the interval cancer[3] rate was between 35% and 50%, and few cases of DCIS[4] (Stage 0) were detected. High breast density and the fast progression rate of breast cancer are the primary reasons for the poor performance of mammography among high-risk women (Warner et al., 2012). The addition of MRI to mammography to screen the high-risk population is worth exploring as it may well address the limitations of mammography since MRI has a sensitivity ranging between 71% and 88.8% while mammography has a sensitivity ranging between 30.7% and 43% (Moore et al., 2009; Warner et al., 2012).

1.6.2 MRI Screening

Unlike mammography, magnetic resonance imaging does not use ionizing

[2] Invasive Cancer: Cancer which spreads outside the original tumour to the surrounding healthy tissue (National Cancer Institute, n.d.e).

[3] Interval cancer: a cancer detected between screening cycles (Public Health Agency of Canada, 2006)

[4] DCIS: Ductal Carcinoma in situ that is defined as abnormal located in the inner coating of a breast milk duct and that has not metastasized outside the duct. It is considered Stage 0 according to the (Canadian Cancer Society, 2010).

radiation. Instead it uses the magnetic features of protons in breast tissue. With this technology, a low percentage of the protons in the patient are drawn into alignment with the strong magnetic field generated within the MRI scanner. These protons are then subjected to a brief radiofrequency energy pulse and this displaces their magnetic vectors. As these protons become "relaxed" and are realigned along the magnetic field that is applied, there is a release of energy. This energy, which is an electromagnetic resonance signal, is identified and is processed electronically in order to construct an image, which involves the exploitation of the different "relaxation times" of the various breast tissues in order to generate contrast in the images (Enriquez & Linitisky, 2009). MRI screening requires around 40 minutes while film mammography needs only 20 minutes to be done (Health Quality Ontario, 2010).

1.6.2.1 MRI Drawbacks

It is difficult to overlook the expense of using MRI which is roughly 10 times greater than mammography (Warner et al., 2012). This expense includes the costs of the unnecessary additional examinations needed to examine the increased number of false positive results produced by MRI screening as a result of its lower specificity relative to mammography (90% versus 95%) (Moore et al., 2009).

Beyond the financial implications, the psychological repercussions of false positives are significant (Warner et al., 2012). According to an investigation recently conducted by Toronto-based researchers (Spiegel et al., 2011), women brought back for supplementary testing as a result of an MRI anomaly were found to be experiencing elevated anxiety associated with breast cancer relative to those who had not been brought back. It has been determined that these women's anxiety drops to a baseline level

after the benign character of the anomaly has been ascertained (Spiegel et al., 2011).

MRI screening is not suitable for people with claustrophobia, or for obese people. Furthermore, the machine is very noisy and the patients have to remain still for a long period (20 to 90 minutes), which makes the screening process difficult and uncomfortable for them (National Breast Cancer Center, 2006).

It is not practical to employ MRI to screen the women population as a whole due to its elevated cost, limited availability and comparatively low specificity. On the other hand, the application of MRI to members of a particularly high-risk demographic group is probably more suitable because the progression rate of breast cancer and the density of breast tissue within this group of women are higher (Warner et al., 2012; Tilanus-Linthorst et al., 2007).

Warner et al. (2008) demonstrated that the combination of both MRI and mammography is more sensitive than MRI alone. In all experienced screening centers, MRI is also more sensitive for DCIS. However, given the fact that the sensitivity of MRI is dependent on the expertise of a screening center's staff in reading the MRI results, there are a few cases of invasive cancer and of low-grade DCIS picked up by mammography but not by MRI, as revealed in some studies such as MARIBS (2006) and Kriege et al. (2004). Given this reason and given the fact that mammography is the only screening strategy that has been proven to decrease breast cancer mortality, magnetic resonance imaging is not currently recommended as a substitute for mammographic screening but rather is recommended as a supplementary technique (Warner et al., 2005; Warner et al., 2012).

1.7 Expansion of the Ontario Breast Screening Program

The Ontario Breast Screening Program (OBSP) provides mammography breast-cancer screening to women in Ontario who are aged 50 and above and who are considered to be at high risk. This program is financially sustained by the Ministry of Health and Long-Term Care and is managed through Cancer Care Ontario in collaboration with local hospitals and other health facilities (The Ottawa Hospital, n.d, Ministry of Health and Long-Term Care, 2009).

In July 2011, the province of Ontario decided to expand the provincial screening program by adding MRI screening to mammography, specifically to screen high-risk women who are 30 to 69 years old. This decision was made based on clinical evidence and on reviews of several studies, as well as on Cancer Care Ontario recommendations. However, no cost-effectiveness study was performed in Canada. (Ministry of Health and Long-Term Care, 2009).

Moreover, in 2010 the Ontario Health Technology Advisory Committee provided guidelines and recommendations to include breast MRI screening and mammography in an organized program that delivers consistent follow-up and treatment to members of the high-risk population. The program expansion started on July 1, 2011 (Ministry of Health and Long-Term Care, 2009).

The greater incidence among high-risk women substantially increases the value of regular screening for this vulnerable group. Since conventional mammography screening does not perform well among high-risk women because of their high breast density (according to many studies), the National Comprehensive Cancer Network (NCCN) has recommended adding MRI as an adjunct to mammography in an effort to increase overall sensitivity and early detection. (Ministry of Health and Long-Term Care, 2009).

1.8 Study Rationale

While many studies have been conducted to evaluate the clinical effectiveness of adding MRI screening to mammography for members of the high-risk populations, only a few cost-effectiveness studies were found in the literature (Medical Advisory Secretariat, 2010; Moore et al., 2009). Most of these economic evaluations of MRI screening were conducted in either the United States or Europe (Dunfield & Severn, 2007). Furthermore, most of these studies did not take into account the impact of the addition of MRI screening on the patients' treatment and associated costs. Accordingly, the findings of these studies do not provide an accurate evaluation of the screening interventions (Ahern, 2008).

In the 2007 Canadian Agency for Drugs and Technologies in Health (CADTH) report, no Canadian cost-effectiveness studies of the addition of breast MRI screening to mammography were identified (Dunfield & Severn, 2007). Given the differing cost levels and health-care system characteristics between countries, it may not be feasible to extrapolate findings from other countries to Canada (Norman et al., 2007; Dunfield & Severn, 2007). Thus, it would appear to be worthwhile to undertake an economic evaluation that relates specifically to Ontario, Canada.

1.9 Study Objective

The overall goal of this research thesis is:

- To assess the cost-effectiveness off adding MRI to mammography screening for early detection among women of the high-risk population in Ottawa by using conventional values for the society's/government's willingness to pay for one life year gained (US$50,000/ LYG (Weinstein, 2008)). Due to the paucity of Canadian health economic evaluation studies on adding MRI to screening mammography in organized breast cancer screening program, this study would add new knowledge and contribute to the literature.

2. LITERATURE REVIEW

2.1 Benefit of Adding Breast MRI to Mammography for Screening High-risk Women

2.1.1 Clinical Effectiveness

A 2012 systematic review entitled Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer (Warner et al., 2012) examined 12 comparative studies of combining MRI and mammography screening (Kuhl et al., 2005; MARIBS, 2006; Kriege et al., 2004; Warner et al., 2001; Warner et al., 2004; Tercate et al., 2003; Hartman et al.,2004/Kurian et al., 2004; Isaacs et al., 2004/Lehman et al., 2004; Lehman et al., 2005; Podo et al., 2002/Sardanelli et al., 2004; Rosen et al., 2004; Riedl et al., 2004).

The systematic review concluded that MRI screening has significantly higher sensitivity than mammography screening alone. This conclusion was also supported by other studies that were not included in the review, such as Leach et al. (2005), Hagen et al. (2007) and Passaperuma et al. (2012). A meta-analysis was also conducted in the systematic review (Warner et al., 2012) based on eight out of 12 studies included (Kuhl et al., 2005; MARIBS, 2006; Kriege et al., 2004; Warner et al., 2004; Hartman et al., 2004/Kurian et al., 2004; Isaacs et al., 2004/Lehman et al., 2004; Lehman et al., 2005; Sardanelli et al., 2004) in order to determine the rates of true positives, false positives, true negatives and false negatives. According to the meta-analysis, the sensitivity and specificity of mammographic examinations combined with MRI were 87.4% and 94.2% respectively. This means that the screening of women at high risk using MRI as a supplement to mammographic examinations leads to measurable increases in sensitivity (36.8% sensitivity for mammography alone) and to a moderate decline in specificity (97.1% specificity for mammography alone). Furthermore, even though MRI screening probably

decreases the rate of mortality from breast cancer, conclusive evidence does not yet exist in the scholarly literature (Warner et al., 2012).

2.1.2 Cost-effectiveness

Economic evaluations are studies conducted to assess and measure the clinical impact and cost of the interventions or programs being compared in order to provide the decision makers with "value for money" estimations of the interventions or programs (CADTH, 2006).

There are five types of economic evaluations: cost-utility analysis (CUA), cost-effectiveness analysis (CEA), cost-minimization analysis (CMA), cost-benefit analysis (CBA), and cost-consequence analysis (CCA). The determination of the most appropriate form of economic evaluation is contingent on the research question, the study objective and the data availability (CADTH, 2006).

In a cost-utility analysis (CUA), results are assessed as health-related preferences, and are typically expressed in terms of the gain in Quality Adjusted Life Years (QALYs). This form of analysis is effective when the Health Related Quality of Life (HRQL) and the life span are impacted by the interventions (CADTH, 2006).

In a cost-effectiveness analysis (CEA) a particular form of economic assessment is performed whereby the results are measured in terms of natural (health) units. The most common units include lives saved, life years gained, and clinical events completed or avoided (CADTH, 2006).

In a cost-minimization analysis (CMA), comparators are equivalent in terms of clinical impact but are different in terms of costs. Accordingly, this evaluation conducted to determine which intervention has the lowest cost (CADTH, 2006).

A cost-benefit analysis (CBA) attributes monetary values to outcomes and costs. These values are typically determined based on the willingness to pay threshold, specifically by means of conjoint analysis or contingent valuation (CADTH, 2006).

In a cost-consequence analysis (CCA), the results and costs of the alternatives are grouped separately in a format that is disaggregated (e.g., hospital costs, intervention costs, adverse events, and clinical benefits) (CADTH, 2006).

In regard to the addition of MRI screening to the OBSP, economic evaluation is crucial because the cost of this screening is considered to be the largest obstacle to implementation. The literature includes only a few studies that have been conducted to determine the cost-effectiveness of MRI and most of these studies were conducted in Europe or the United States. According to the 2007 report of the Canadian Agency for Drugs and Technologies in Health (CADTH) entitled "Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer," only four studies were identified in the literature review (Dunfield & Severn, 2007, CADTH, 2006).

One of these studies, conducted in Italy by Podo et al. (2002) (abstract only), indicated that seven cases of breast cancer were detected by MRI and were missed by mammography. Based on these results, the authors concluded that MRI breast screening is cost-effective at a willingness-to-pay threshold of €6,000 (CAN$9,042) per additional breast cancer detected (Podo et al., 2002).

According to a one-year British research study (Grebisch et al., 2006) in which the performance metric was the rate of cancer detection, the expense associated with integrating MRI with mammographic screening

was over £28,000 (CAN$51,200) for each breast tumour found in carriers of the BRCA1/2 genetic mutation, in relatives of the first degree or in individuals with a family history of ovarian or breast tumours, and was over £15,000 (CAN$27,429) for carriers of BRCA2 only. Their sensitivity analysis revealed that the MRI examination cost was the most significant factor having a negative impact on cost-effectiveness but that the rates of additional MRI tests and of recall in general also affected the outcomes. Staff costs, equipment and maintenance costs, consumables costs, contrast medium and overhead/ capital costs, and screening and further investigations costs were considered in this study. On the other hand, treatment costs were not considered even though these costs might have a significant impact on the cost-effectiveness of MRI screening. Neither life years gained nor QALYs were considered in the study as outcome measures (Grebisch et al., 2006).

Another British cost-utility study on MRI screening (Norman et al., 2007) was conducted exclusively on carriers of the BRCA1 mutation. A Markov model was developed to determine the cost/QALY of each screening strategy considered, which included mammography alone, MRI alone and the combination of MRI and mammography, with 100 high-risk women being selected to participate in the hypothetical cohort. The study results indicated that the cost/QALY of adding MRI to mammography for women aged 30 to 39 was £13,486 (CAN$24,628) and for women aged 40 to 49 was £7,781 (CAN$14,209). Screening by MRI alone was dominated by the combination of MRI and mammography. According to the sensitivity analysis in this study, the variable that most affected the result was the average five-year survival rate. In general, based on a £20,000 (CAN$36,524) willingness-to-pay threshold, the study found that the probability that combining MRI and mammography screening will be cost effective is 80% among women aged 40 to 49 years, and is 63% among

women aged 30 to 39 years. Since this study considered only BRCA1 women and since the progression rate among these women is very high according to Tilanus-Linthorst et al. (2007), this result may not be easily generalized to other high risk women. For simplicity and due to the lack of data, it was assumed that the cost of treatment is the same regardless of the stage of breast cancer. This assumption regarding treatment does not accurately reflect real clinical practice and may lead to an underestimation of treatment costs. It was assumed that women would remain in treatment for two years. The financial value of patients' work time lost was not considered in this study. Only the utility values of not receiving screening and of receiving screening (MRI, mammography and the combination of both screening) were considered in this study while other important values were disregarded, including the disutility from having breast cancer, receiving chemotherapy, receiving radiation therapy or having breast reconstruction (Norman et al., 2007).

An American economic analysis (Plevritis et al., 2006) developed and implemented a model based cost-effectiveness study that compared mammographic screening by itself with the combination of magnetic resonance imaging and mammographic screening. The increase in the number of quality-adjusted life years (QALYs) as a result of the different types of screening was used as the metric for effectiveness. The assessment was performed using a hypothetical group of women with the BRCA1/2 genetic mutation who were followed over the course of their lifetime by means of a Monte Carlo simulation. A sophisticated mathematical model of the natural progression of invasive breast cancer was employed to determine the incidence rate of the disease and its associated mortality. The expenses were premised on the reimbursement costs for U.S. Medicare and on other sources from the literature (Plevritis et al., 2006).

It was found that the cost per QALY gained was US$88,651 (CAN$97,312) using MRI screening for carriers of the BRCA1 mutation and was US$188,034 (CAN$206,405) for carriers of the BRCA2 mutation aged between 25 and 69. The sensitivity analysis indicated that the cost for each QALY was impacted by the patients' age and by the MRI cost. The lowest cost for each QALY was US$43,484 (CAN$47,732) for carriers of the BRCA1 mutation aged between 40 and 49. Furthermore, magnetic resonance imaging was proven to deliver higher cost-effectiveness in instances of elevated breast-cancer risk. The cost for each extra QALY was US$41,183 (CAN$45,207) for carriers of BRCA1 and was US$98,454 (CAN$108,073) for carriers of BRCA2 through the provision of MRI services to women who have very high breast density and who are below 50 years old. For each extra QALY, the cost was US$55,420 (CAN$60,835) for carriers of the BRCA1 mutation and was US$130,695 (CAN$143,464) for carriers of the BRCA2 mutation who were between 35 and 54 years of age (Plevritis et al., 2006).

The authors came to the conclusion that, at a threshold of US$100,000 (CAN$109,770) for each additional QALY, the combination of MRI and mammography on an annual basis is cost-effective for all of the carriers of BRCA1 between the ages of 35 and 54 and for BRCA2 carriers who are insensitive to mammographic testing. MRI testing every two years was found to be cost-effective at that threshold for all carriers of BRCA2. The authors also came to the conclusion that the combination of MRI and mammographic examinations was not cost-effective, at the same threshold, among women between the ages of 25 and 34 years and among older women above age 55. In this study, both direct and indirect costs were considered. Direct treatment costs were considered according to Estrogen-Receptor status (positive/negative) in addition to metastatic breast-cancer treatment, mastectomy with reconstruction (unilateral =

US$31,387 (CAN$34,454), bilateral = US$47,081 (CAN$51,681)) and ovarian cancer treatment. This was the only study reviewed that considered the treatment cost of ovarian cancer (US$108,514 (CAN$119,116)) and the median annual surveillance costs after therapy for primary breast cancer (US$544 (CAN$597)). Moreover, indirect costs, defined as the cost of time lost from work, were considered for screening, further investigation and treatment, which made the cost per life year gained produced by this study one of the highest among all the studies reviewed. Moreover, although the utility values resulting from having breast cancer treatment are a very important measure, they were not considered in the study (Plevritis et al., 2006).

Another study from the U.S. was undertaken in 2009 by Taneja et al. to analyze the cost-effectiveness of magnetic resonance imaging both with and without mammographic testing among high-risk women. The researchers created a simulation model to identify the effects of screening with MRI and/or mammography for groups of 10,000 women with BRCA1 and BRCA2 mutations on the one hand and for women with other high-risk factors on the other hand. The model predicted the number of women who were accurately and inaccurately diagnosed under each strategy, the lifetime effects from the standpoint of the extra care required, patient utilities, life expectancy and QALYs. Cost-effectiveness was characterized in terms of the cost for each additional QALY (Taneja et al., 2009).

Among the 400 women (from a total of 10,000) carrying BRCA1/2 mutations and unidentified breast tumours, 361 cases were identified using both MRI and mammography combined, 290 cases were identified using MRI alone and 160 cases were identified using mammography alone. False positives respectively totaled 1,526, 1,190 and 528. The cost

for women with BRCA1/2 mutations for each additional QALY achieved through the combination of MRI and mammography in comparison with mammography alone was US$25,277 (CAN$27,747). Among other high risk women, the cost of each additional QALY acquired through the combination of MRI and mammography in comparison with mammography alone varied according to the prevalence of breast cancer between US$45,566 (CAN$50,018) (for 300 cases) to US$310,616 (CAN$340,963) (for 50 cases). The cost-effectiveness of MRI by itself was similar to the cost-effectiveness of mammography by itself. The research study concluded that the screening of women with BRCA 1/2 mutations by means of MRI – by itself or together with mammography – is cost-effective according to current standards when compared with mammography by itself. Among women with other high-risk factors, MRI might also be economically efficient, and the degree to which this is the case is a function of the anticipated breast cancer prevalence when screening occurs. Only direct costs were considered in the study which means that the cost of the time lost from work was disregarded. Since only four categories were considered to calculate the costs of breast cancer treatment (DCIS, no nodal involvement, nodal involvement and metastatic disease), none of which considered the stage of cancer, this might lead to an underestimation of the treatment cost. Health state utilities were considered per age, per breast cancer stage, and per metastactic cancer state. The disutility values associated with having breast screening, further investigations and breast-cancer treatments were not considered in the study (Taneja et al., 2009).

There are two more studies that were not included in the CADTH report (CADTH, 2006). One of these studies is Moore et al. (2009), which was conducted in the United States. In this study, a Markov decision model was developed using a hypothetical cohort of women in order to evaluate the cost-effectiveness of MRI compared to mammography screening for

women who have a lifetime risk of developing breast cancer that is greater than or equal to 15%. The Claus model was used to assess the lifetime risk of developing breast cancer. The model input parameters, including MRI and mammography sensitivity and specificity as well as the utility values for each health state, were taken from the literature. The costs of hospital and physician services were obtained from Medicare reimbursement rates while the medication costs were taken from the Federal Supply Scale. The outcome measure of this study is the cost of each additional QALY resulting from each screening strategy.

According to the study findings, the cost per QALY of receiving MRI compared to mammography was US$179,599 (CAN$197,146). In univariate analysis, when the cost of an MRI was reduced to US$315 (CAN$345), the cost per QALY for MRI screening decreased to US$50,000 (CAN$54,885). In probabilistic sensitivity analysis, magnetic resonance imaging produced -0.202 QALYs (95% central range: -0.767 QALYs to +0.439 QALYs) in comparison with mammography at a willingness-to-pay threshold of US$50,000 per QALY (CAN$54,885). The study concluded that MRI is not cost-effective, even at willingness-to-pay thresholds that are greater than US$120,000 per QALY (CAN$131,724), despite the fact that MRI screening may provide health benefits for some high-risk women (Moore et al., 2009).

The MRI biopsy was not considered in the study as further investigation although it is considered to be the most accurate and expensive biopsy and accordingly is used more often among women with high breast density. Radiation and chemotherapy were considered in addition to Tamoxifen. The breast treatment costs were taken into account based on nodal status and the extension (mainly local therapy and not metastactic cancer) of the tumour but not based on the stage. The treatment costs in this study were obtained from the Federal Supply Scale (FSS), unlike the other U.S.

studies which obtained their cost data from Medicare. That might be the reason for which these costs were slightly lower than treatment costs of other U.S. studies. Other services provided by hospitals and physicians were also considered, such as pre-op evaluations and outpatient visits. The disutility values associated with receiving breast-cancer treatment were not considered in the study. The screening scenario of the combination of MRI and mammography was not considered in the study (Moore et al., 2009).

The second study that was not included in CADTH report was conducted by Lee et al. in 2010. This study was also conducted in the United States. Three screening strategies for a cohort of 25-year-old BRCA1 mutation carriers – film-mammography, MRI, and the combination of MRI and mammography – were compared by means of computer simulation. This approach was employed to assess the QALYs and lifetime costs. The costs and QALYs were extracted from the medical literature and from rates of Medicare reimbursement (Lee et al., 2010, CADITH, 2006).

According to the study simulation, annual screening using both screening modalities compared to mammography alone was the most effective intervention with an incremental cost-effectiveness ratio (ICER) equal to US$69,125 (CAN$75,879) per QALY. Annual MRI screening was excluded by extended dominance because the ICER of MRI compared to mammography alone (US$206,384/QALY (CAN$226,548)) was greater than that of the next most effective screening scenario which is the combination of both methods of screening. The ICER of annual mammography screening as opposed to clinical surveillance by itself was US$16,751 (CAN$18,388) for each extra QALY. The sensitivity analysis demonstrated that, when the cost of MRI escalated to US$960 (CAN$1,054) (with the base case being US$577 (CAN$633)), or the risk of developing breast cancer by age 70 fell below 58% (with the base case being 65%) or when the sensitivity of combined screening fell below 76%

(with the base case being 94%), the cost of adding MRI to mammography exceeded US$100,000 (CAN$109,770) for each additional QALY. The study's authors concluded that the combination of MRI and mammography screening is likely to be cost-effective at a threshold of US$50,000 (CAN$54,885) to US$100,000 (CAN$109,770) per additional QALY. Similar to Norman et al. (2007), this study considered only BRCA1 women and, given the fact that the progression rate among these women in particular is very high, this may lead to increases in the cost-effectiveness of MRI screening compared to a wider screening program that includes other high-risk women. Moreover, this study has the highest cost of adding MRI to mammography per additional QALY (US$69,125 (CAN$75,879)) among all the studies reviewed except Moore et al., 2009 which compared MRI alone with mammography alone. The second highest threshold (US$55,420 (CAN$60,835)) was produced by Plevritis et al. (2006) for the BRCA1 group. In a similar manner to Plevritis et al. (2006), both direct and indirect costs were considered but in a more comprehensive way. But, unlike Plevritis et al. (2006), ovarian treatment costs were not considered. Moreover, instead of considering treatment based on hormonal receptor and metastatic cancer only, this study considered the treatment costs based on three main factors: breast cancer stage (DCIS, local, regional, distant), ER (estrogen receptor) status (negative/positive) and age (<50 years, ≥ 50 years). This classification of treatment more closely aligns with real clinical practice according to the clinical experts. In addition, the indirect costs were more inclusive and encompassed the patient time costs of having surgery, radiation, chemotherapy, hormonal therapy, follow-up visits, informal care, screening and biopsies, as well as the cost of lost wages. In this study, the sensitivity of the screening rates (MRI, mammography and combined screening) were considered based on tumour size. In addition, utility values were considered according to the stage of breast cancer. Similarly,

the utility values associated with having breast cancer treatments were not considered (Lee et al., 2010).

Among the studies mentioned above there are wide disparities among the costs of adding MRI. This difference might be caused by varying the cost estimations in the evaluation of MRI cost-effectiveness (as explained above). Other factors such as the discounting rate, the value that is attributed to one QALY and the degree of variation in MRI sensitivity (because of differences in the experience and expertise of the screening center staff in MRI interpretation) may also cause differences in the cost-effectiveness estimations of adding MRI.

In conclusion, the studies on cost-effectiveness mentioned above provide a mixed picture on the effectiveness of adding MRI to mammography screening for high risk women influenced dramatically by the decisions regarding what costs to include and exclude from the study.

3. METHODOLOGY

3.1 Type of Analysis

According to reasons that will be discussed later in the limitations section of this thesis, a cost-effectiveness analysis was chosen to be conducted through simulation to assess the benefit of adding MRI to mammography for the breast screening of high-risk women using a willingness- to-pay threshold of $50,000/LYG (Weinstein, 2008). The primary cost-effectiveness outcome measure was incremental costs per life years gained (LYG) for women at a high-risk of developing breast cancer who were receiving the combination of MRI and mammography screening versus mammography screening alone. The incremental cost-effectiveness ratio per life year gained (ICER/LYG) was calculated by dividing the difference between the total costs (including screening, further investigation and treatment costs) of the combination of both screening methods

and the total costs of mammography screening alone by the difference between the total life years of women who received both strategies of screening and the total life years of women who received mammography screening only. The costs and life years were accrued over the remaining lifetime of 5,000 30-year-old women for each simulation run.

$$\text{ICER} \frac{\text{Total costs of both screening combined} - \text{Total costs of mammography screening alone}}{\text{Total life years of women who recived both screening} - \text{Total life years of women who recived mammography screening alone}}$$

3.2 Target Audience

The primary target audience in this study is the Ministry of Health and Long-Term Care (MOHLTC), which is the decision-maker for the funding of the prevention program.

3.3 Perspective

Costs were evaluated from the perspective of the health-care system (i.e., the MOHLTC) and only direct costs were considered. Indirect costs were assumed to be constant for both screening modalities. While it is true that the higher rate of false positives with MRI undoubtedly lead to more opportunity costs, it was thought that these differences were not sufficient to undermine the analysis.

3.4 Study Setting

The study was conducted in partnership with the Ontario Breast Screening Program, Hampton Park Plaza Centre in Ottawa, which is one of the facilities participating in the Ontario Breast Screening Program (OBSP) in collaboration with the Ottawa Hospital. This program offers regular screening through biennial mammography tests for women 50 years and over and recently combined MRI with mammography for the annual screening of high-risk women between the age of 30 and 69 years (Public Health Agency of Canada, 2006).

Ethics approval to conduct the study was obtained from the Ottawa Hospital Research Ethics Board (OHREB).

3.5 Study population

Since no women were recruited for the study and since the main purpose of this study was to assess the recent expansion of the Ontario Breast Screening Program (OBSP), we utilized the criteria that were set by the OBSP for women to be eligible to receive both MRI and mammography screening. The simulation model's hypothetical cohort consists of 5,000 women aged 30 who are deemed to be at high risk for breast cancer. "High risk" is defined as women who have one or more of the following characteristics : 1) a genetic mutation known as breast cancer antigen 1 or 2 (BRCA 1 or 2) which can be identified through genetic testing; 2) a child, parent or other close relative who has been identified as having this genetic anomaly; 3) a family history of breast cancer and a greater than 25% probability lifetime risk of at some point developing breast cancer which can be confirmed through genetic assessment; or 4) received radiation therapy to the chest before reaching age 30 as part of a treatment program for another cancer or condition (e.g., Hodgkin's disease) (Ministry of Health and Long-Term Care, 2009; Afonso, 2009). In the study we classified the hypothetical cohort into three subgroups – BRCA1, BRCA2 and women with other high-risk factors – with the proportion of the cohort in each group based on the distribution of these risk types within a sample of 243 high-risk women who attended the Hampton Park Plaza screening centre in Ottawa during the years 2011 and 2012.

3.6 Study Design

Ideally, in order to determine the cost-effectiveness of a new health intervention such as adding MRI to mammography for the breast screening of high-risk women, a clinical trial (CT) would be conducted to observe the overall effects and costs of the intervention. However, clinical trials often are not feasible due to time constraints and/or ethical violations (such as denying women the benefits of

MRI screening). CTs are also expensive and only allow for a limited number of potential scenarios to be tested to the extent that in many cases it is questionable whether the results can be generalized to the whole population. In addition, generalizing from past studies is problematic as data pertaining to costs are not likely to be applied or adequately transferable between countries because of differences in health care systems characteristics and cost levels. Moreover, these data typically do not offer insight into the longer-term results of the adoption of the new technology because the study environment usually is modified according to the research protocol which accordingly does not reflect actual clinical practice (Caro, Möller & Getsios, 2010).

For these reasons, the best alternative to a clinical trial is a simulation model because it can be used to assess and compare a wide range of strategies and scenarios with minimal cost and without violating any ethical considerations. Moreover, simulation modeling allows further projection of the evaluation results based on data from the literature within a short time frame. Furthermore, uncertainty in the model parameters can be handled in a systematic way by means of univariate and multivariate sensitivity analysis. Through this analysis, parameters that have a high impact on the cost-effectiveness of a technology can be determined (Menn & Holle, 2009). The most common types of decision models in health economics are decision trees, Markov models and discrete-event simulation (DES) models. Discrete-event simulation (DES) was chosen for this study due to its ability to handle the complexity of breast-cancer screening, treatment and survival because these events can be modeled in any order with no restrictions and because time in this type of simulation model is continuous (unlike in Markov model simulation which requires specific time intervals and mutually exclusive events or health states) (Karnon et al., 2012; Menn & Holle, 2009; Institute for Quality and Efficiency in Health Care, 2009).

More specifically, Arena software was chosen over other modeling software tools to implement the DES simulation because of its graphical interface and modeling-specific functions which facilitate the design and implementation of the breast-cancer screening and treatment process (Menn & Holle, 2009).

3.7 Simulation Model

3.7.1 Discrete-Event Simulation Model Overview

A DES model was developed to evaluate the cost-effectiveness of adding MRI screening to mammography for the screening of high-risk women in Ottawa. Two annual screening scenarios were compared: (a) mammography alone, and (b) the combination of mammography and MRI. Based on the annual incidence of breast cancer, screening features, breast-cancer progression among high-risk women, treatment and breast-cancer survival rates, the model simulates women progressing from age 30 to 100 and calculates the accumulated life years and costs in order to predict the cost of one life year gained by each screening strategy.

To assess the robustness of the simulation findings, 30 replications of 5,000 simulated women each were run for each screening scenario and for the variations of each parameter included in the univariate analysis in order to determine the confidence interval of the ICER.

The model parameters and corresponding data sources and assumptions are summarized in Table 2 and are described below. (See the model framework in Appendix A, and the simulation model input parameters data in Appendix B)

3.7.2 Analytical Time Horizon

The life time horizon, until the women died from breast cancer or other causes or else reached the age of 100, was chosen to capture important life-savings effects.

3.7.3 Cost Estimations and Discounting Rate

Only direct costs were considered in the model. These costs are as follows:

1. Screening costs:
    - MRI screening cost
    - Digital mammography screening and additional diagnostic mammographic imaging costs
    - Costs of both forms of screening combined
2. Further investigation costs:
    - Ultrasound screening and ultrasound biopsy
    - Mammography screening and stereotactic biopsy
    - MRI biopsy
3. Treatment costs including the costs of Herceptin plus chemotherapy and hormonal therapy were included differentiated by the presence of Estrogen receptors (ER), human epidermal growth factor receptor 2 (Her2) status and nodal status.

These costs include physicians' and other health-care professionals' time, equipment, and supply costs. On the other hand, other direct costs, such as hospital stays, outpatient and emergency visits, and capital costs, could not be included in our study because of limitations in the available data. Accordingly we assumed that these costs are similar for the two screening modalities. However, if better data become available in the future it will be worthwhile to consider these costs to determine their impact on the cost-effectiveness of adding MRI. All study costs are presented in

Canadian dollars. These costs were not discounted because, as a result of inflation in medical expenditures, these costs might increase in the future in accordance with continuous improvements of health technologies and treatments which accordingly will affect the validity of any attempted discounting (Villanti et al., 2013). Moreover, given the fact that the main purpose of discounting is to allow for comparability between study results in the future and given the fact that no solid evidence can be found in the literature on which discounting rates should be considered, each study applies different discounting rates to their results which accordingly undermines comparability between findings (Treasury Board of Canada Secretariat, 2007). However, the impact of the discounting rate was assessed by means of sensitivity analysis and was varied to reflect discount rates of 3% and 5%. (See Table 2 for a list of cost items included)

3.7.4 Life Years Gained

Life years gained were calculated by subtracting the total age of the women who received the combination of both forms of screening from the total age of the women who received mammography screening only in order to determine the difference in life years gained between receiving the combination of both forms of screening on the one hand and mammography screening alone on the other hand. We used screening by mammography alone as a reference to determine the costs and benefits associated with the addition of MRI screening. Since health-benefits discounting is widely controversial, the life years gained were not discounted (Parsonage & Neuberger, 1992).

We used life years gained instead of QALYs in our simulations primarily because we assumed that women who develop breast cancer will either die or be cured following one year of treatment. If they survive treatment

then they re-enter the annual screening program. Given this assumption, it did not seem reasonable to employ QALYs as the outcome measure.

3.7.5 Base-case Analysis

At the beginning of the simulation, the model created a hypothetical cohort of 5,000 women who are 30 years old. The women in the cohort were divided into the three subgroups (BRCA1, BRCA2 and other high risk) based on the distribution of these risk types within the sample of women who received screening from the Hampton Park Plaza Centre in Ottawa during the years 2011 and 2012. The hypothetical cohort was assumed to not have chosen any preventive/risk-minimization interventions such as Tamoxifin, prophylactomy, mastectomy and so forth, primarily because there was insufficient evidence found in the literature regarding the impact of these interventions on the lifetime risk of developing breast cancer. Furthermore, it was assumed that this cohort of women has no previous history of breast cancer. Within the simulation, women develop breast cancer based on the annual incidence rate of breast cancer within the three high-risk groups obtained from the literature (see Table 2 for data sources and assumptions).

Each screening modality's sensitivity rate, defined as the rate of correctly detecting cancers, was used to determine whether the cancer is correctly detected (true-positives). Screening costs were accumulated for all the women in the simulation and, in the cases where breast cancer was detected by mammography only, additional mammographic diagnosis costs were added. If the screening modalities were unable to detect the cancer (based on the sensitivity rate), then it was assumed that the tumour was an interval cancer and would be detected by other means (usually mammography or MRI) before the next screening cycle. This assumption was made based on the rapid growth rate of tumours among high-risk

women. Once the cancer has been detected (either through screening or as an interval cancer), further investigations including a biopsy are performed to verify that the cancer is indeed present. In clinical practice, further investigations start with an ultrasound because it is the least costly test. If the ultrasound is able to detect the tumour, then an ultrasound biopsy is performed. If the ultrasound is not able to detect the tumour, then an additional mammography test is performed. If mammography is able to detect the tumour, then a stereotactic biopsy is performed. Finally, if a stereotactic biopsy does not succeed, then an MRI biopsy is performed. However, in the simulation, the hypothetical cohort received further investigation based on the probability of having the test, which was calculated based on the frequency of each test within the sample of women who attended the Ottawa Hospital during the years 2012 and 2013. Both screening methods detected tumours and interval tumours were classified into four tumour size categories: DCIS, ≤10 mm (small), 11-20 mm (medium) and > 20 mm (large). The distribution of screening detected tumours' sizes per screening modality and the distribution of the size of interval cancers was obtained from the literature. (See Table 2 for data sources and assumptions)

The specificity of each screening modality, defined as the rate of negative results produced by the screening modality when in fact there is no cancer to detect, was used to determine the rate of false positives (1- specificity). Women with false positives proceeded to receive further investigation (as described in the previous paragraph). The probability of having these investigations was calculated based on the false positive rate for each test. An assumption was made that one of these biopsies would eventually determine that the cancer was a false positive. The additional costs related to unnecessary further investigations were added. Women who did not develop breast cancer during the screening cycle will either die from other

causes or will have to restart screening. (See Table 2 for data sources and assumptions)

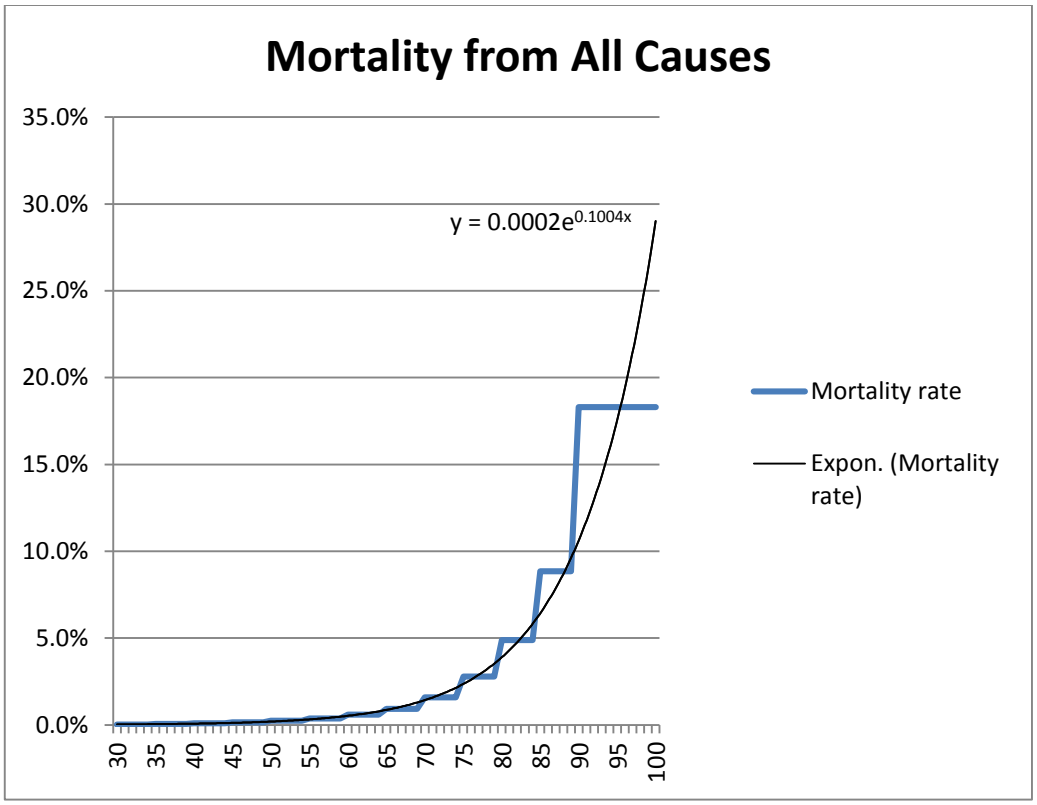
Women who have developed breast cancer (either screening detected or interval cancer) will either choose to be treated or undergo a mastectomy. The percentage of women who developed breast cancer and choose mastectomy (10%) was obtained from clinical expert Dr. Ellen Warner because of the lack of data available in the literature (E. Warner, personal communication, October 12, 2012). Based on the available data we assumed that, when women choose mastectomy, both breasts are removed and the risk of developing breast cancer is eliminated. In reality, not all women who develop breast cancer (10%) choose to undergo mastectomy. Some of these women (around 50% of them) choose to undergo lumpectomy followed by radiation therapy. Since no solid evidence was found in the literature on how many women select lumpectomy plus radiation, we only considered mastectomy with breast reconstruction (J. Seely, personal communication, June 10, 2014). For those women who chose mastectomy, only the cost of mastectomy with reconstruction was added and the women stayed in the simulation until they died from other causes. They did not re-enter the screening program and are assumed to have no chance of recurrence. It was assumed that all women who choose to undergo mastectomy decide to proceed with breast reconstruction. However, in reality there is a minority who do not. The lack of specific data on the percentage of women who choose breast reconstruction was the basis on which we assumed that all of the women who undergo mastectomy proceed with breast reconstruction (J. Seely, personal communication, June 10, 2014). See Table 2 for data sources and assumptions)

The rest of the women who have developed breast cancer (either screening detected or interval cancer) and have refused mastectomy will accrue treatment costs that are estimated based on the following factors: the presence of Estrogen receptors (ER), the human epidermal growth factor receptor 2 (Her2) status and the nodal status of the tumour. According to Dr. Warner, these are the main factors that affect the treatment plan (E. Warner, personal communication, December 10, 2012). These factors were assigned to the cohort according to their distribution among the three risk groups (BRCA1, BRCA2 and other high risk) for both screening detected and interval cancers as obtained from the literature. (See Table 2 for data sources and assumptions)

The probability of death from breast cancer was calculated based on the five-year survival rates that were obtained from the SEER database (Gloeckler Ries & Eisner, n.d.). Given the fact that, according to the evidence from the literature, both tumour size and nodal status are known to have a significant impact on the survival rate of women, the breast-cancer death rates were calculated based on nodal status (positive, negative) and tumour size (Michaelson et al., 2003; Carter et al., 1989).. (See Table 2 for data sources and assumptions)

The probability of death from all other causes according to age was taken from the Morbidity and Mortality in Ottawa report, 2012 (Ottawa Public Health, 2012). An exponential distribution was applied to the death-rate data to make the death rate from all causes increase yearly instead of based on an interval of every five years as given in the report (Figure 5).

Figure 5: Exponential distribution of death rate from all causes



It was assumed in the simulation that a woman with breast cancer will be cured and will re-enter screening after one year of treatment unless she dies from breast cancer or other causes or unless she chooses to undergo mastectomy. We made this assumption because no evidence was found in the literature on the specific percentage of breast recurrence after treatment and thus these women are treated in the same fashion as other high risk women who have not yet developed breast cancer. If it was shown that the recurrence rate is significantly different then the model could easily be adapted to that reality.

During the simulation, women who reach 69 years are no longer qualified to receive the combination of MRI and mammography screening.

Accordingly, the life expectancy of women after the age of 69 was added to those women in order to capture the benefit of life years gained caused by the addition of MRI screening. (See Table 2 for data sources and assumptions)

In the following table, all the key parameters that were used in the simulations are encapsulated, along with information on their sources and on the relevant assumptions that were used.

Table 2: Model parameters, data sources and assumptions

Parameter	**Data source**	**Any major assumptions and limitations**
The starting age of the hypothetical cohort is 30	Ministry of Health and Long-Term Care, 2009	According to OBSP, annual MRI and mammography breast screening are provided to high-risk women between the ages of 30 and 69 years.
Type of high risk	Hampton Park Plaza screening centre, Ottawa	Three groups of high-risk women were considered in the study: BRCA1, BRCA2 and other high risk. The distributions of these three groups were taken from the data provided by Hampton Park Plaza screening centre based on a sample of 243 high-risk women who attended the centre during the years 2011 and 2012.
Development of breast cancer among high-risk women	Antoniou et al., 2003	Only the annual incidence rates of breast cancer by age of both BRCA1 and BRCA2 women were available in the literature. Accordingly, since the progression rates of breast cancer are similar for BRCA2 and other high-risk women

Parameter	Data source	Any major assumptions and limitations
		according to Tilanus-Linthorst et al. (2007), it was assumed that the incidence rates are similar for both groups.
Cancer correctly detected through screening (true positives)	Warner et al., 2012 (meta-analysis)	The sensitivities of screening were used to determine the true positive results with sensitivity being defined as the ability of screening to identify cancer when it truly exists. Two values of sensitivity were entered into the model: mammography and both screening methods combined. The sensitivity of mammography was based on film rather than digital mammography (which is currently used at the Hampton Park Plaza screening centre and the Ottawa hospital) because no data are available in the literature on the sensitivity of both MRI and digital mammography screening combined. Accordingly we cannot compare the sensitivity of digital mammography alone with the sensitivity of both MRI and film mammography combined. Due to the lack of data, it was assumed that the sensitivities of screening modalities are the same regardless of the age, tumour size and breast density of the women.
Cancer detected by mammography	Warner et al., 2012 (meta-analysis)	In the cases where women received both MRI and mammography screening combined, according to the clinical expert Dr. Seely, cancers detected by mammography alone need

Parameter	Data source	Any major assumptions and limitations
		additional diagnostic mammography (J. Seely, personal communication, September 18, 2012). To calculate the number of these cancers, the sensitivity of MRI was subtracted from the sensitivity of both methods of screening combined.
Interval cancers		All cancers that developed but were not detected by screening were assumed to be interval cancers. It was assumed that these cancers would be detected before the next screening cycle due to the fast progression rate among high-risk women.
The size of the interval tumour	Fracheboud et al., 1999	The sizes of interval cancers detected were categorized into: DCIS, ≤ 10 mm (small tumour), 11-20 mm (medium tumour), >20 mm (large tumour). The probability of detecting interval cancer from these four tumour size categories were calculated according to: $\frac{\text{No.of interval cancers detected (from a specific tumor size category)}}{\text{Total number of interval cancers detected}}$ These data were provided based on sample drawn from the general population. The age interval of the study sample was 50-69, which is clearly different from the age interval of our study. Furthermore, the data were published in 1999 and thus the women in the study only received mammography breast screening.

Parameter	Data source	Any major assumptions and limitations
Further investigations which include: • Ultrasound which may suggest ultrasound biopsy • Mammography which may suggest stereotactic biopsy • MRI biopsy	The Ottawa Hospital	In the model, the hypothetical cohort of women was distributed among these tests based on the probabilities of women receiving these tests. These probabilities were calculated based on the frequencies of these tests that were provided by Hampton Park Plaza centre and by the Ottawa Hospital to all women (both high and average risk) who attended the screening centre during the years 2011 to 2012. $\frac{\text{Frequency (of a specific test)}}{\text{Total frequencies of all tests}}$
The size of the tumour at time of detection	Warner et al., 2004; MARIBS Study Group, 2006; Scheuer et al., 2002	The cancers detected for each screening scenario (mammography alone versus both screening methods combined) from the three studies were combined by adding the number of cancers detected and by grouping them into four categories: DCIS, ≤ 10 mm (small tumour), 11-20 mm (medium tumour), > 20 mm (large tumour). The probabilities of detecting cancer from these four tumour size categories were calculated according to: $\frac{\text{No.of cancers detected (from a specific tumor size category)}}{\text{Total number of cancers detected (by each screening senarios)}}$

Parameter	Data source	Any major assumptions and limitations
		Then the probabilities of detecting cancer from the four tumour size categories and for each of the two screening scenarios were entered into the model.
Cancer falsely detected at screening (false positives)	Warner et al., 2012 (evidence-based report)	False positive rates , which defined as detecting cancer by the screening modality when it is not exist in reality, for each screening scenario were calculated based on the specificity of screening as follows: 1 - specificity. Two values were entered into the model: 1 - specificity of mammography only, and 1 - specificity of both screening methods combined. The specificity of mammography was based on film mammography rather than on digital mammography because no data are available in the literature on the specificity of both MRI and digital mammography screening combined. Accordingly we cannot compare the specificity of digital mammography alone with the specificity of both MRI and film mammography combined. Due to the lack of data, it was assumed that screening modality specificities are the same regardless of the age, tumour size and breast density of the women.

Parameter	Data source	Any major assumptions and limitations
Ultrasound falsely suggests ultrasound biopsy	Weinstein et al., 2009	The probability of a false positive ultrasound was calculated as 1 - specificity of the ultrasound.
Mammography falsely suggests stereotactic biopsy	Warner et al., 2012 (evidence-based report)	The probability of false positive mammography was calculated as 1 - specificity of the mammography.
Tumour histology (ER, HER2 status)	Passaperuma et al., 2012	The distribution of ER, HER2 receptors per BRCA1 and BRCA2 risk groups was entered into the model. There were no data on the receptor distribution within the other high-risk group. Accordingly, the distribution of ER and HER2 within the other high-risk group was assumed to be equal to the distribution of the receptors among BRCA2 women since they have similar tumour progression rates (Tilanus-Linthorst et al., 2007). Only ER and HER2 receptors were considered in the model as they are believed to have the major impact on the treatment of breast cancer according to clinical expert Dr. Ellen Warner (E. Warner, personal communication, December 10, 2012).
Nodal status (positive, negative)	Taneja et al., 2009	The distribution of nodal status per risk group (BRCA1, BRCA2 and other high risk) and per screening modality was entered into the model. Only data on the nodal status distribution for

Parameter	Data source	Any major assumptions and limitations
		MRI alone and for mammography alone were given in the study. For that reason we assumed that nodal distribution for MRI screening is equal to the nodal distribution for both screening methods combined. This assumption may lead to underestimation of the benefit of receiving both screening methods combined.
Percentage of women who refuse mastectomy	E. Warner, personal communication, October 12, 2012	Women with breast cancer who choose to undergo a mastectomy were assumed to no longer require screening and to have no chance of developing breast cancer. Thus, the remaining life years are estimated based on the age of the patient at time of the mastectomy and are added to the life years of the patient before exiting the model. On the other hand, women who refuse a mastectomy receive treatment and then re-enter the screening program. Due to the lack of data in the literature, this percentage was obtained from Dr. Warner.
Death from all causes	Ottawa Public Health, 2012	The probability of death from all cases per age (from 30 to 100 years) was calculated as follows: $$\frac{\text{Female death rate per a specific age}}{\text{Total population } (= 100{,}000)}$$ The mortality rate from all causes in the Ottawa Morbidity and Mortality report was calculated

Parameter	Data source	Any major assumptions and limitations
		based on the general population rather than based on high-risk women, but we assumed that women at high risk have a similar rate of death from all causes. An exponential distribution was applied to the death-rate data to make the death rate from all causes increase annually instead of at five-year intervals as given in the report.
Life year expectancy of women after the age of 69	Ottawa Public Health, 2012	To calculate the life expectancy of women after they reach the age of 69, we added a constant value of life years (17 years) based on the expected remaining life years of women who reached the age of 70.
Death from breast cancer	Gloekler Ries & Eisner, n.d. (the SEER database) Silverstein, 1998	The death rate from breast cancer was calculated based on the five-year survival rate per tumour size, classified into four categories: DCIS ≤ 10 mm (small tumour), 11-20 mm (medium tumour), > 20 mm (large tumour), and per nodal status (negative, positive). According to the following: Breast cancer mortality rate = 100 – survival rate Survival data taken from SEER were based on the general population of American women. Although these data are from the U.S., they were used in this study because no Canadian data were found that considered survival rates per tumour size and nodal status. The U.S. data were

Parameter	Data source	Any major assumptions and limitations
		used based on the assumption that these data are reflective of the survival rates of Canadian women. Additionally, we assumed that these survival rates are similar for high-risk women since survival from breast cancer is mostly dependent on the size and histology of the tumour at the time of detection and not on the risk type.
Cost Parameters		
Screening costs	Based on sample of women who attended Ottawa hospital during the years of 2011 to 2012	The costs of mammography alone and of both MRI and mammography combined including costs of physicians and clinical staff services, building and equipment costs were entered into the model.
Costs of additional diagnostic mammography	Based on sample of women who attended Ottawa hospital during the years of 2011 to 2012	Additional diagnostic mammography is usually needed when the tumour is detected by mammography screening alone. Accordingly cost of additional diagnostic mammography including costs of physicians and clinical staff services, building and equipment costs were included in the study model.
Cost of further investigation	Based on sample of	The cost of ultrasound screening, ultrasound biopsy, mammography screening, stereotactic

Parameter	Data source	Any major assumptions and limitations
	women who attended Ottawa hospital during the years of 2011 to 2012	biopsy and MRI biopsy including costs of physicians and clinical staff services, building and equipment costs were entered into the model.
Mastectomy with breasts reconstruction costs	Ministry of Health and Long-Term Care, 2013	The cost of mastectomy with reconstruction was obtained from the OHIP schedule and benefits. The total cost of the main reconstruction surgeries was added to the radical mastectomy cost as this was by far the most common choice and the most expensive option.
Treatment costs	Based on sample of women who attended Ottawa hospital during the years of 2011 to 2012	The costs of treatment including costs of physicians and clinical staff services, building and equipment costs were entered into the model per ER, HER2 and nodal status. In the opinion of clinical expert Dr. Ellen Warner, these are the most important factors that should be considered to determine the type of treatment that should be provided to the patient (E. Warner, personal communication, December 10, 2012).

3.7.6 Simulation Validation

The inputted parameters for the simulation model were all based on either the best available evidence in the literature or else on real data from the OBSP. The logic of patient flow throughout the modeled was thoroughly vetted by clinical experts.

In addition, two attributes were chosen for comparison with real data from the literature in order to validate the model simulation. These two attributes are life expectancy and the percentage of women who developed breast cancer. By comparing the numbers that resulted from the simulation and the numbers that resulted from the literature, we can conclude that the simulation model accuracy is acceptable (Table 3).

Table 3: Simulation results compared with real data from the literature to validate the simulation model

Attributes	**Simulation results**	**Data from the literature**
Life expectancy	**Mammography only:** 82 years (95% CI 82 - 83 years) **Both MRI and mammography:** 83 years (95% CI 83-83 years)	83 years[5]
Percentage of women who developed breast cancer	38.80% (95% CI 38.52%-39.08%)	36.85%[6]

4. RESULTS

4.1 Base-case Scenario

The results of the simulation of the hypothetical cohort of 5,000 high-risk women over their lifetime (after the age of 30) indicated that the combination of both MRI and mammography screening provided 416,476.15 years at a cost of

[5] Statistics Canada, 2012

[6] Dunfield & Severn, 2007

CAN$172,408,358.68 while mammography screening alone provided 412,664.03 years at a cost of CAN$45,742,505.26 (Table 4). According to these results, the addition of MRI to mammography for the breast screening of high-risk women increased the total life years gained but at a cost. The ICER of both screening methods compared to mammography alone was CAN$36,079.32 per life year gained (95%CI ±4572.79), which means that the addition of MRI to mammography is a cost-effective intervention according to the commonly used willingness-to-pay threshold of US$50,000 (CAN$54,885) per life-year gained (Table 4).

Table 4: Total cost, total life-years, and the incremental cost-effectiveness ratio of the two screening scenarios

	Total life years	**Total cost (CAN$)**	**Incremental cost per life year gained (ICER/LYG)**
Mammography screening only	412,664.03 years	CAN$45,742,505	N/A
Both screening methods combined	416,476.15 years	CAN$172,408,359	CAN$36,079.32/LYG (95%CI ± 4,572.79)

For the simulation results set out above, the tumour size distribution at the time of detection per screening modality was obtained from the combination of three studies (Warner et al., 2004; MARIBS Study Group, 2006; Scheuer et al., 2002). These data indicated that mammography is better than both MRI and mammography screening combined in terms of early detection – a result that is both counter-intuitive and contrary to clinical experts' opinion. The main reason behind this limitation is the small sample size of the available studies that contain

data on tumour size at the time of detection by mammography and by the combination of both screening methods. More specifically, the MARIBS study group indicated that mammography is better than MRI in terms of detecting DCIS (MARIBS Study Group, 2006).

To overcome the limitations of these data and to try to capture the benefits of adding MRI to mammography screening, we assumed that both screening strategies (mammography alone and both screening methods combined) result in the same distribution for tumor size at the time of detection (which was classified as: DCIS, ≤10mm, 11-20 mm, >20mm). The probability of a cancer being detected at a specific tumour size by a particular screening strategy was thus calculated by combining the data from all screening types into a single distribution. However, the distribution of the tumour size of interval cancers, which was obtained from Fracheboud et al. (1999), was significantly different. As one would expect, these cancers were detected at a much larger size than screening detected cancers (Table 5).

Table 5: The assumed tumour size distribution of screening-detected tumours and the distribution of interval cancers per screening strategy

Screening strategy	**DCIS**	**≤ 10 mm (small)**	**11_20 mm (medium)**	**>20 mm (large)**
Mammography	21.3%	40.9%	26.7%	11.1%
Both screening combined	21.3%	40.9%	26.7%	11.1%
Interval cancers	2.1%	12.2%	43.9%	41.7%

According to this assumption, the ICER of mammography compared to both screening methods was CAN$30,043.48 per life year gained (95%CI ±2524.40) (Table 6). This assumption caused a statistically significant reduction in the cost per life year gained (LYG) according to the paired t-test (P <0.05). We considered that assumption to be a base-case scenario. In all likelihood, the addition of MRI improves on early detection and thus the assumption that both screening strategies have the same tumour size distribution at the time of detection will cause us to underestimate the benefit of adding MRI.

Table 6: Total cost, total life-years, and the incremental cost-effectiveness ratio of the base-case analysis

	Total life years	**Cost (CAN$)**	**Incremental cost per life year gained (ICER/LYG)**
Mammography screening only	412,277.08 years	CAN$45,679,655	N/A
Both screening methods combined	416,695.67 years	CAN$172,443,728	CAN$30,043.48 (95% CI ±2524.40)

4.2 Sensitivity Analysis

Univariate sensitivity analysis was performed on the key parameters believed to have the most impact on the simulation results. Wherever possible, these key parameters and the ranges used in the sensitivity analysis were determined based on the review of the literature (Table 7). The sensitivity analysis was conducted by entering the key parameters' variations into the model and re-running the simulation. Paired t-tests were used to determine whether or not the key parameters' variations are statistically significant.

Table 7: Key parameters considered in the sensitivity analysis and their variations

Parameter	Base-case	Variations
Sensitivity rate • Mammography • Both screening combined	Based on Warner et al., 2012: • 36.8% • 87.4%	Based on Warner et al., 2012, two scenarios were considered for mammography only screening: • 31% and 43% Based on Warner et al., 2008, two scenarios were considered for both methods combined screening: • 80% and 100%
False-positive rate (1-specificity) • Mammography • Both screening combined	Based on Warner et al., 2012: • 2.90% • 5.80%	Based on Warner et al., 2008, two scenarios were considered for each screening strategy: • 1% and 6% • 3% and 10%
Distribution of tumour size at time of detection	Based on data that were obtained and combined from three studies (Warner et al., 2004; MARIBS Study Group, 2006; Scheuer et al., 2002)	Three assumptions were made for tumours detected by both screening methods combined: 1. 5% of the tumours from each tumour size classification are detected one stage earlier. 2. 10% of the tumours from each tumour size

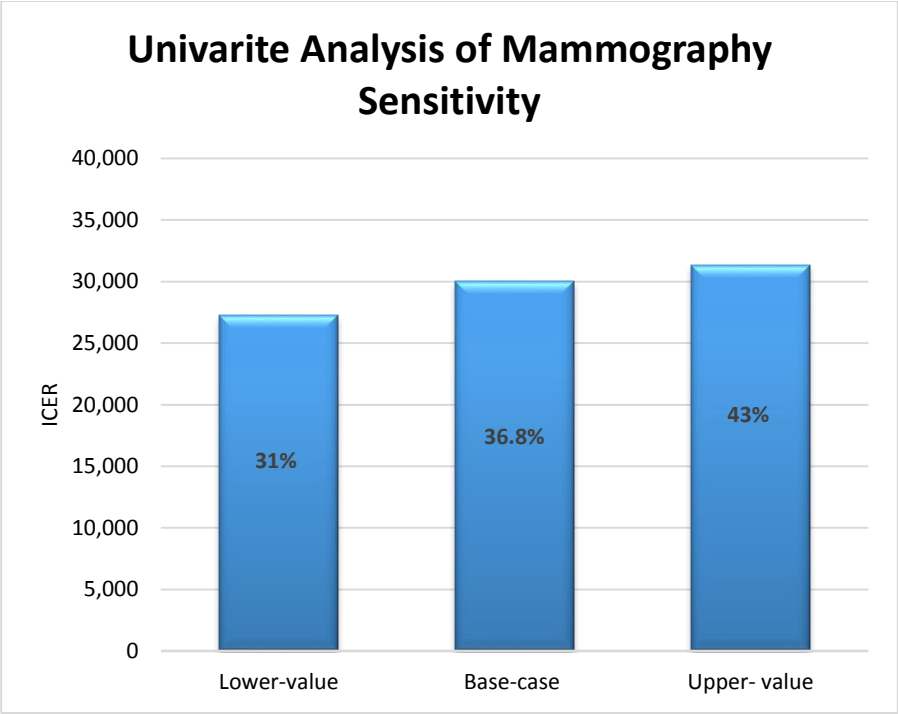
Parameter	Base-case	Variations
		classification are detected one stage earlier. 3. 20% of the tumours from each tumour size classification are detected one stage earlier. (See appendix C-1) The tumour size distribution at the time of detection by mammography screening alone stayed the same as in the base-case scenario.
Screening and further investigations cost: • MRI screening • Mammography screening • Additional diagnostic mammography • Both screening methods combined • Ultrasound • Ultrasound biopsy	Based on data obtained from the Ottawa Hospital	Based on Norman et al., 2007: Increased and decreased the screening and further investigations cost by 20%. (See appendix C-2)

Parameter	Base-case	Variations
• Stereotactic biopsy • MRI biopsy		
Treatment and mastectomy cost	Based on data obtained from the Ottawa Hospital and Ministry of Health and Long-Term Care, 2013	Based on Norman et al., 2007: Increased and decreased treatment and mastectomy costs by 20%. (See appendix C-3)
Discount rate	0%	Two discounting rates were chosen: 3% and 5%
Type of high risk	BRCA1/2 and other high risk	Only genetic mutation carriers (BRCA1/2). (See appendix C-4)
Percentage of women who chose mastectomy	10%	20%
Breast cancer annual incidence	Based on data from Antoniou et al., 2003	Breast cancer incidence rate increased by 1% and 2%.(See appendix C-5)
Nodal status	Based on data from Taneja et al., 2009	Based on data from Lee et al., 2010: Nodal distribution was increased by 25% and by 50%. (See appendix C-6)
Breast cancer mortality	Gloekler Ries & Eisner, n.d. (the SEER database)	It was assumed that the mortality rate of both node positive and negative tumours decreased by 20% for the small (≤10 mm) tumours, by 10% for medium size (11-20

Parameter	Base-case	Variations
		mm) tumours and by 5% for large (>20 mm) tumours. On the other hand, the mortality rate for DCIS tumours remained the same since it is equal to zero. (See appendix C-7)

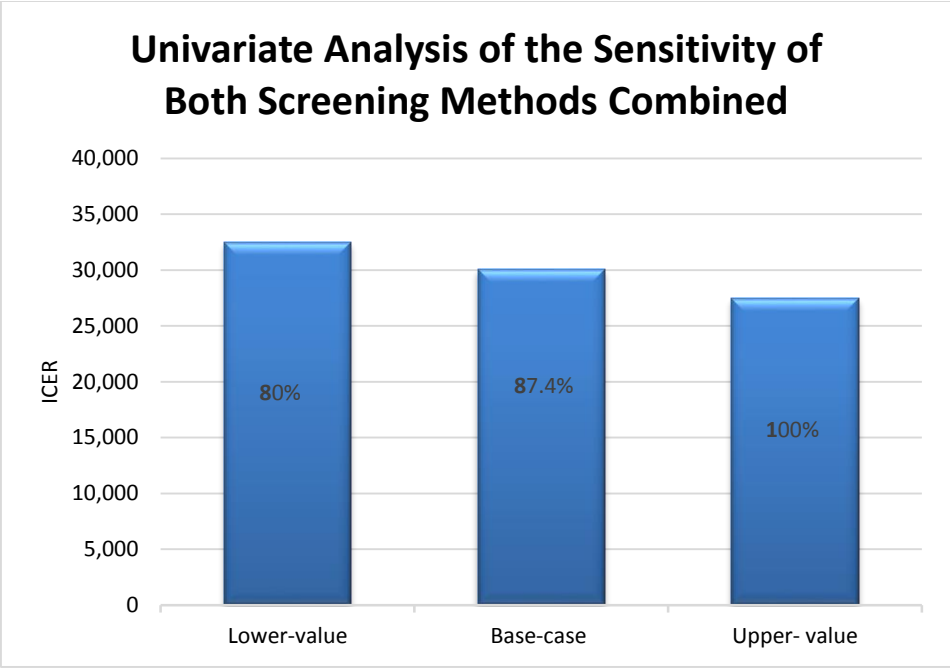
The first parameter considered in the univariate sensitivity analysis is the sensitivity of the two screening modalities. Two alternative values, upper and lower, were chosen for each screening modality (mammography: 43% and 31%; both screening methods: 100% and 80%). These values were determined based on the two systematic reviews conducted by Warner et al. in 2012 and by Warner et al. in 2008. As the mammography sensitivity increased to 43%, the benefit of MRI decreased. Accordingly, the upper value of mammography sensitivity increased the ICER to CAN$31,342.10/LYG (95% CI ±2138.02) (Figure 6). Meanwhile, when mammography sensitivity decreased to 31%, the ICER (CAN$27,237.23/LYG; 95% CI ±1736) decreased and the addition of MRI became more cost-effective (Figure 6).

Figure 6: Univariate analysis of the mammography sensitivity rate



On the other hand, as the sensitivity of the combination of both screening methods increased to 100%, the ICER per life year gained decreased (CAN$27,444.86/LYG; 95% CI ± 2,531.58) and thus the addition of MRI became more beneficial (Figure 7). Whereas when both screening sensitivities decreased to 80%, the ICER (CAN$32,492.57/LYG; 95% CI ±2797) increased and the MRI addition became less beneficial (Figure 7).

Figure 7: Univariate analysis of the sensitivity rate of the combination of both screening methods

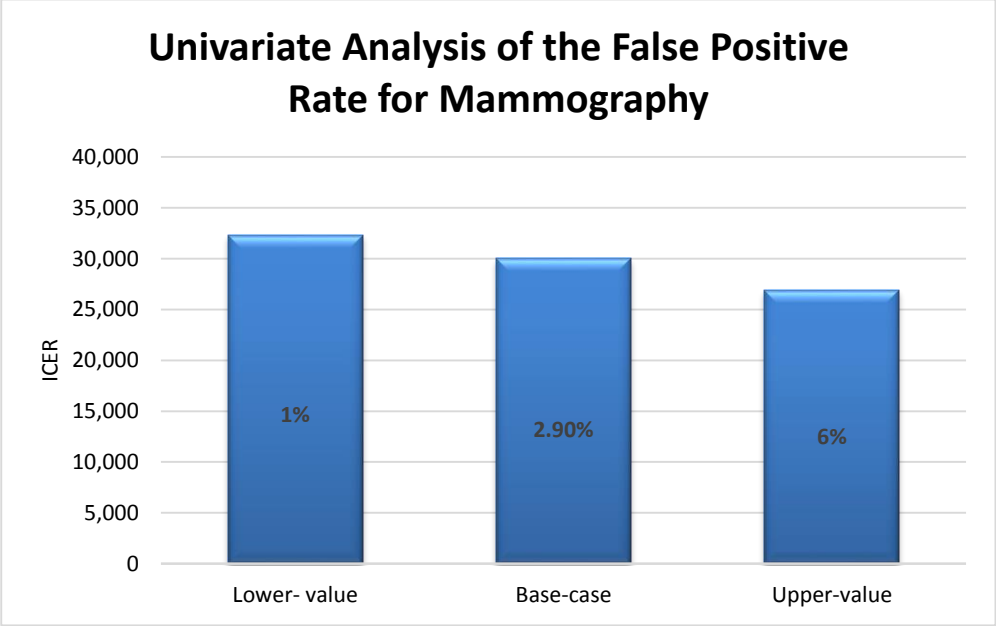


The impacts of the variation in the sensitivity rates of the screening scenarios (mammography alone and both screening methods combined) on the cost-effectiveness of the addition of MRI are statistically significant according to the paired t-test (P <0.05), except for the upper bound of mammography sensitivity (P = 0.4). It is clear that the variations in the sensitivity of mammography and of both screening methods combined had a minimal impact on the ICER due to the narrow range of values used according to the findings of the systematic reviews.

The second parameter considered in the sensitivity analysis is the false positive rate. Similarly, upper and lower variables were chosen for each screening scenario (mammography: 6% and 1%; both screening methods: 10% and 3%) based on the systematic review conducted by Warner et al. in 2008. As the false positive rate of mammography was increased to 6%, the ICER dropped to CAN$26,929.24/LYG (95% CI± 1687.17) (Figure 8). On the other hand, when the false positive rate of mammography was decreased to 1%, the ICER increased

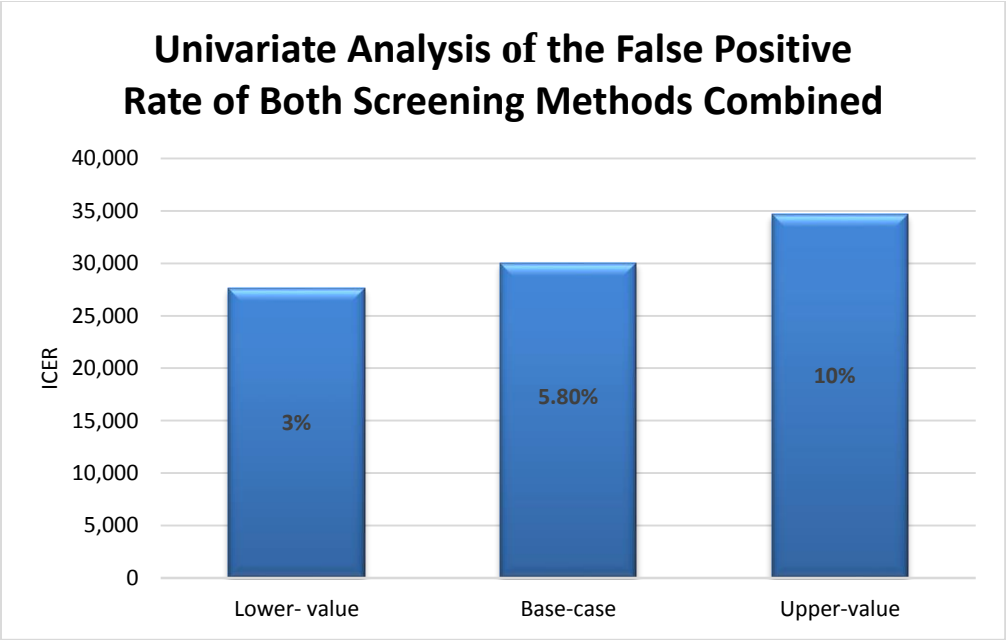
to CAN$32,328.35/LYG (95% CI±3182) and the addition of MRI became less effective (Figure 8).

Figure 8: Univariate analysis of mammography false positive rate



Increasing the false positive rate of the combination of both screening methods increased the ICER to CAN$34,663.18/LYG (95% CI±4763.55), which accordingly reduced the cost-effectiveness of the addition of MRI (Figure 9). On the other hand, reducing the false positive rate of the combination of both screening methods decreased the ICER to CAN$27,640.05/LYG (95% CI±2116) (Figure 9)

Figure 9: Univariate analysis of the false positive rate of the combination of both screening methods

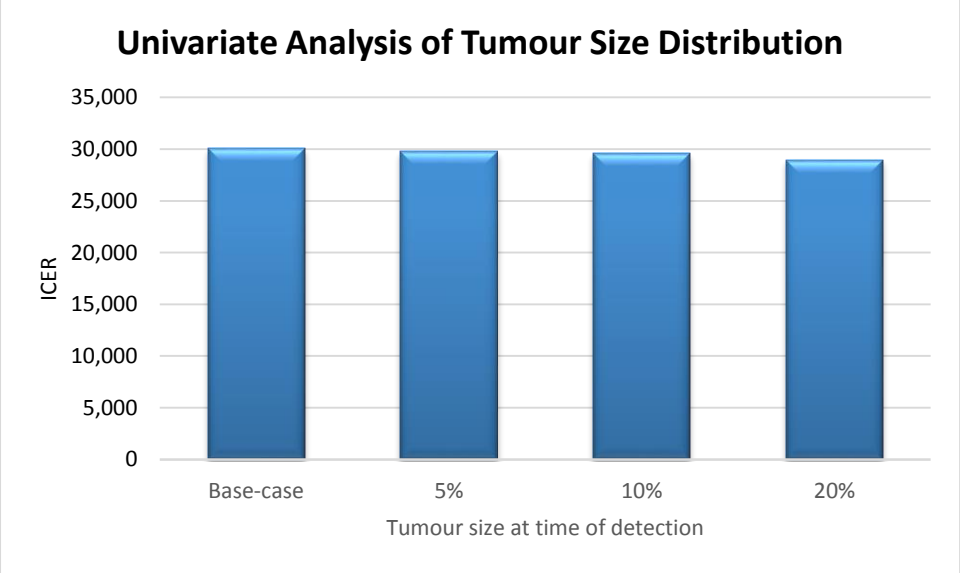


According to the paired t-test, false positive rate variations have a statically significant impact on the cost-effectiveness of MRI (P <0.05), except on the false positive rate of the lower value of mammography (P = 0.1). Similarly, the variations in the false-positive rates of mammography and of both screening methods combined had a minor impact on the ICER due to the relatively narrow range of values used according to the findings of the systematic reviews.

The third parameter included in the univariate analysis is the distribution of tumour size at the time of detection. Three assumptions were made to assess the effect of tumour-size distribution at time of detection by the combination of both screening methods on the cost-effectiveness of the addition of MRI. The first assumption was that 5% of the tumours from each tumour size classification (DCIS, ≤10mm, 11-20 mm, >20mm) are detected one stage earlier when using the combination of both screening methods (ICER = CAN$29,758.10/LYG; 95% CI± 2,486.15). The second assumption is that 10% of the tumours from each tumour size classification are detected one stage earlier (ICER = CAN$29,592.82/LYG; 95% CI± 2,513.41). The third assumption is that 20% of

the tumours from each tumour size classification are detected one stage earlier (ICER = CAN$28,954.86/LYG; 95% CI± 2,300.69). The tumour size distribution at the time of detection by mammography screening alone stayed the same as in the base-case scenario (Figure 10).

Figure 10: Univariate analysis of tumour size distribution at the time of detection



The results of the simulation based on the previous assumptions indicated that increasing the rate of early detection through the combination of both screening methods increased the cost-effectiveness of MRI addition to mammography. According to the paired t-test, the distribution of tumour size at the time of detection by screening has a statistically significant impact on the cost-effectiveness of the addition of MRI ($P< 0.05$). It is clear, however, that the impact of tumour size at the time of detection is not dramatic according to our study data. This is largely because tumour size is not nearly as crucial as it once was due to improved treatment options so that even larger tumours do not result in death.

The fourth parameter considered is the costs of screening and further investigation that were obtained from the Ottawa Hospital. Based on Norman et al. (2007), these costs were increased by 20% (ICER=CAN$36,071.29/LYG; 95% CI± 11856.51) and decreased by 20% (ICER=CAN$24,015.67/LYG; 95% CI± 2017.17). When the cost of screening and further investigation increased, the cost-effectiveness of MRI decreased due to MRI's lower specificity. The cost variations of screening and further investigation have a statistically significant impact on the cost-effectiveness of the addition of MRI according to the paired t-test (P <0.001). Nonetheless, the effect of increasing the cost of further investigations is not likely to be considerable as the improved performance of a screening centre's staff in reading the MRI results will likely bring the specificity of MRI up close to that of mammography.

The fifth parameter is the costs of breast-cancer treatment and mastectomy that were obtained from the Ottawa Hospital and the 2013 OHIP schedule and benefits (Ministry of Health and Long-Term Care, 2013). Similarly, based on the previous study by Norman et al. (2007), the treatment costs were increased by 20% (ICER=CAN$30,024.37/LYG; 95% CI± 2,522.02) and decreased by 20% (ICER=CAN$ 30,062.6/LYG; 95% CI± 2,526.99). When the treatment and mastectomy costs were increased, the benefit of MRI increased because of its contribution to early detection of the tumour before nodal involvement. However, the effect of the variation of treatment and mastectomy costs on the cost-effectiveness of the addition of MRI is marginal and is not statistically significant according to the paired t-test (P >0.05).

The sixth parameter considered is the discounting rate. In the base-case analysis, all the costs were not discounted (for the reasons discussed earlier in this thesis). In order to assess the impact of discounting on the cost-effectiveness ratio, the simulation was run with discount rates of 3% (ICER=CAN$17,890.76/LYG; 95% CI±1,289.1) and 5% (ICER=CAN$13,390.19/LYG; 95% CI±965.97). Variation

in the discount rate has a statistically significant impact on the cost-effectiveness of the addition of MRI according to the paired t-test ($P< 0.001$). According to these results, the discount rate has a huge impact on the ICER for the addition of MRI because we only discounted the costs (the numerator), not the life years gained (the denominator).

The seventh parameter considered is the type of women eligible for screening with MRI in the simulation. In the base-case scenario, three groups of high-risk women were considered: BRCA1, BRCA2 and other high risk. The distributions of these three groups were taken from the data provided by the Hampton Park Plaza screening centre. However, in order to determine if the risk type has an impact on the cost-effectiveness of MRI, only genetic mutation carriers (BRCA1/2) were considered in the univariate analysis. Similarly, data on the distribution of BRCA1/2 only was obtained from the Hampton Park Plaza screening centre. Considering genetic mutation carriers only, there was an increase in the cost-effectiveness of the addition of MRI (ICER=CAN$24,671.86/LYG; 95% CI±1886.02). The ICER increase is statistically significant according to the paired t-test ($P< 0.001$).

The eighth parameter considered is the percentage of high-risk women who choose to undergo mastectomy. In the base-case scenario, the percentage of women who chose mastectomy was 10% according to the clinical expert (E. Warner, personal communication, October 12, 2012). In the univariate analysis, we assumed that the percentage will increase in the future as a result of increasing awareness among high-risk women. Increasing the percentage to 20% decreases the cost-effectiveness of MRI (ICER=CAN$31,646.56/LYG; 95% CI±2090.7). However, the impact of the percentage of women who choose to undergo mastectomy on the cost-effectiveness of the addition of MRI is not significant according to the paired t-test ($P> 0.05$). Although it is expected that the percentage of women who choose mastectomy will increase in the future, this

increase is not anticipated to be dramatic due to the side effects of permanently losing the breast and due to the improvement of screening and treatment which make them better alternatives than mastectomy. Accordingly, the impact of increasing the percentage of women who choose to undergo mastectomy on the ICER of the addition of MRI is minimal.

The ninth parameter considered is the incidence of breast cancer. In the base-case, the assumption was made that the rate of incidence is the same as its current level through the years while, according to the data obtained from the literature, breast cancer increased over the years largely as a result of screening (Brown, 1992). For this reason, we assumed that the incidence rate increased by 1% in order to estimate the lower value (ICER=CAN$30,045.2/LYG; 95% CI±2,565.1) and increased by 2% in order to estimate the upper value (ICER=CAN$30,113.84/LYG; 95% CI±2,882.2). According to the paired t-test, such small changes in the incidence rate has no significant impact on the cost-effectiveness of MRI (P> 0.05). The increase in the breast-cancer incidence rate has only a marginal effect due to the minor anticipated variations in these rates.

The tenth parameter included in the univariate analysis is the nodal status distribution. Based on the nodal status distribution range from the Lee et al. (2010) study, the nodal distribution was increased by 25% as a lower value (ICER=CAN$24,663.70/LYG; 95% CI± 1,634.5) and by 50% as an upper value (ICER=CAN$20,954.35/LYG; 95% CI± 1,094.9). Increasing the rate of nodal involvement, particularly the upper value which entails increasing the nodal involvement by 50%, has a relatively large impact on the ICER. The main reason for this is that the breast-cancer treatment costs and the mortality rate considered in the simulation were significantly affected by the nodal involvement. When the nodal involvement increased, the cost-effectiveness of MRI increased as well, mainly because the addition of MRI screening contributes to early detection of

the tumour before nodal involvement has begun. The effect of nodal status distribution was statistically significant according to the t-test ($P< 0.001$).

The last parameter that was considered in the univariate analysis is the breast-cancer mortality rate. Based on the literature, breast-cancer mortality has been steadily decreasing due to improvements in treatment. For this reason, the simulation was run with for a scenario where the mortality rate of both node positive and negative tumours decreased by 20% for small (≤10 mm) tumours, by 10% for medium (11-20 mm) tumours and by 5% for large (>20mm) tumours. The mortality rate for DCIS tumours remains the same since it is equal to zero. Decreasing the breast-cancer mortality rate significantly decreased the cost-effectiveness of the addition of MRI (ICER=CAN$32,390.6/LYG; 95% CI± 2,831.7) according to the paired t-test (P< 0.001). It is clear that decreasing the mortality rate has a slight effect on the ICER due to the minimal variations used for these rates since the mortality rate has already decreased significantly due to improvements in screening and treatment during the last years.

The findings of the sensitivity analysis indicate that the impact of the parameter variations on the cost-effectiveness of adding MRI to mammography for the breast-screening of high-risk women is statistically significant for most scenarios explored. However, the degree of change in the ICER is not hugely impactful as in all cases the ICER remained well below the commonly used willingness-to-pay threshold of $50,000 per life year gained.

5. DISCUSSSION

The findings of our study, conducted from the perspective of the health-care system, suggest that the screening of high-risk women can be improved through the addition of MRI to mammography screening at a reasonable cost.

Among the studies in the literature regarding the cost-effectiveness of the addition of MRI, the closest direct comparison with our results is the cost-utility modeling study conducted by Taneja et al. (2009). The findings of Taneja et al. (2009) indicated that the cost of each additional QALY achieved through the addition of MRI to mammography for BRCA1/2 women was US$25,277 (CAN$27,539), which is comparable with our result of CAN$24,672 per life year gained for genetic mutation carriers only. However, unlike our study, the costs and benefits in Taneja et al. (2009) were discounted by 3%. If we compare the 3% discounted ICER for the three high risk group instead of the genetic mutation carriers only from our study (CAN$17,890.76/LYG) with Taneja et al. (2009) ICER (CAN$27,539/QALY), we can notice that the difference in ICERs is significant. This is mainly due to the screening and further investigations costs considered in Taneja et al. (2009) being generally higher than the costs considered in our study. Other differences exist between the two studies such as the outcome measure - cost/QALY for Taneja et al. (2009) versus cost/LYG in our study. The QALY in Taneja et al. (2009) was calculated by combining estimations of life expectancy and patient utilities including age-specific utilities, having breast cancer and having metastatic cancer. In addition, in Taneja et al. (2009), the incremental benefit was calculated for BRCA1/2 women as one group and for other high-risk women as another group. In our study's base-case scenario the ICER was calculated for all three high-risk groups combined (BRCA1, BRCA2 and other high risk). However, we estimated the impact of considering BRCA1/2 women only on the cost-effectiveness of the addition of MRI through a univariate sensitivity analysis. Furthermore, regarding the estimation of the treatment cost, Taneja et al. (2009) considered costs based on nodal status, DCIS and metastatic tumour while in our study we estimated the treatment cost based on nodal status and ER, HER2 status, which is closer to the real clinical practice according to the opinion of clinical experts (E. Warner, personal communication, December 10, 2012).

Taneja et al. (2009) modeled one year of ongoing screening while our study chose a life time horizon. Despite the differences between our study and Taneja et al. (2009), the results from both studies are roughly comparable.

On the other hand, other economic evaluation studies in the literature pertaining to the addition of MRI have major differences with our study in terms of the outcome measure chosen as well as the model structure and assumptions, all of which may help explain the discrepancies between their result and ours. Overviews of these studies are discussed below.

Podo et al. (2002) (abstract) and Grebisch et al. (2006) chose cost per breast cancer detected as an outcome measure while in our study cost/LYG was chosen as the outcome measure. In addition, Grebisch et al. (2006) applied a 3.5% annual discounting rate to the costs and health benefits while in our study costs and health benefits were not discounted in the base-case scenario but 3% and 5% discounting rates were applied to the study costs only in the univariate sensitivity analysis. Moreover, Grebisch et al. (2006) did not include treatment-related costs in their analysis which may be the main reason underlying the high cost of adding MRI (£28,000; CAN$51,200/ breast cancer detected) provided in that study in comparison with our study (3% discounted ICER= CAN$17,890.76/LYG).This difference can be attributed to the fact that MRI screening contributes to the early detection of breast cancer before nodal involvement, which accordingly reduces treatment costs and increases the cost-effectiveness of the addition of MRI to mammography. Likewise, screening and further investigations costs that were included in Grebisch et al. (2006) are much higher than our study costs.

Norman et al. (2007) considered BRCA1 women only and assumed that the treatment cost remains constant regardless of the stage of breast cancer, which does not reflect actual clinical practice and underestimates the benefit of adding MRI. Costs and benefits were discounted by 3.5% in this study unlike the base-case scenario of our study which was not discounted. The cost per QALY for different age groups was considered as an outcome measure. According to the study, the cost per QALY of adding MRI to mammography is £13,486 (CAN$24,628) for women aged 30 to 39 years and £7,781 (CAN$14,209) for women aged 40 to 49 years. Cost per QALY of the younger group (30 to 39 years) is higher than our 3% discounted ICER (CAN$17,890.76/LYG), while the

cost per QALY of the older group (40 to 49 years) is slightly lower than ours. The primary reason behind this is that breast cancer is usually more common among the older age group, but it has a faster progression rate among the younger group and since Norman et al. (2007) does not consider the treatment per breast cancer stage at the time of detection, then the study could not capture the benefit of adding MRI screening among the younger age group.

Plevritis et al. (2006) conducted an economic evaluation from a social perspective while in our study only the health-care system perspective was considered. In terms of the estimation of treatment costs, only receptor status and metastatic breast cancer were considered as well as the cost of ovarian cancer treatment. This is quite different from the treatment classification that was considered in our study. In Plevritis et al. (2006) costs and QALYs were discounted by 3%. The cost per QALY for BRCA1 women and BRCA2 women separately was considered as an outcome measure. The cost per QALY produced by Plevritis et al. (2006) (US$88,651; CAN$97,312 for BRCA1 and US$188,034; CAN$206,405 for BRCA2) was significantly higher than the 3% discounted ICER of our study (CAN$17,890.76/LYG). This is mainly because screening, further investigations and treatments costs that were considered in Plevritis et al. (2006) are much higher than the costs were included in our study.

Moore et al. (2009) compared the cost per QALY of MRI alone with mammography screening alone. Unlike our study, screening with the combination of MRI and mammography and screening of the genetic mutations carriers were not considered in Moore et al. (2009). In this study, costs and health benefits were discounted by 5%. According to the study, the cost per QALY of breast MRI compared to mammography was US$179,599/QALY (CAN$197,146), which is dramatically higher than our study's 5% discounted ICER (CAN$13,390.19/LYG) as well as the other studies mentioned above. Similarly, costs of screening, further investigations and treatments considered in this study are much higher than costs included in our study.

In Lee et al. (2010), only BRCA1 genetic mutation carriers were considered while in our study BRCA1/2 and other high-risk women were included. Both costs and QALYs in this study were discounted by 3%. The main outcome measure considered in Lee et al. (2010) was cost per QALY which is equal to $69,125 (CAN$75,879) compared to our study's 3% discounted ICER (CAN$17,890.76/LYG). Although the treatment cost estimates were very similar in Lee et al. (2010) and in our study, the difference between the ICERs of the two studies is significant. This is mainly because the costs of screening, further investigations and treatments that were considered in Lee et al. (2010) are much higher than the costs considered in our study.

Generally, costs of screening, further investigations and treatments in previous studies are much higher than the costs included in our study, but there is no adequate explanation was found of how these costs were considered which making it difficult to determine the main reasons behind the large differences between previous studies' ICERs and ours.

6. STUDY LIMITATIONS

Our study has some limitations that should be addressed. One of these limitations is that the cost of hospital stays, emergency visits, day procedures, capital costs and indirect costs, such as the cost of the time lost from work, were not included in our model because of insufficient data currently available in the literature. Accordingly, it was assumed that these costs would remain constant regardless of the type of screening employed. In reality, the addition of MRI may reduce treatment time through early detection and thus the addition of these costs might increase the cost-effectiveness of the MRI addition.

Moreover, preventive interventions such as Tamoxifin, chemoprevention and prophylactic mastectomy were not considered in the study due to insufficient published data on the extent to which these interventions reduce the risk of developing breast

cancer. If these interventions were to reduce the risk of developing breast cancer substantially, they might eventually make the addition of MRI less cost-effective (Pelvritis et al., 2006).

In our study, estimates of parameters that specifically apply to high-risk women were used whenever possible. Nonetheless, in some situations we based the input parameter estimates on samples drawn from the population as a whole (Lee et al., 2010). For example, given the paucity of data in the literature on mortality rate according to nodal status and tumor size among women at high risk, the five-year breast-cancer survival rate within the overall population (drawn from the SEER database) was employed to determine the death rates from breast cancer among high-risk women. The justification is that a patient's survival is more a reflection of the stage of the tumour than of the risk factor. The SEER data led us to the conclusion that the involvement of nodes has the greatest influence on rates of survival. Furthermore, based on the recent study by Gareth et al. (2014) among BRCA1/2 carriers, the difference is not significant in terms of the rates of survival between the combination of both screenings on the one hand and mammography alone on the other hand. The study used only a small sample size and did not provide the survival rates based on tumour size and nodal status, factors that according to the literature have a significant influence on survival (Gareth et al., 2014). As a result of these limitations we were not able to use these data in our model.

Similarly, data on interval cancers were obtained based on a sample of the general population between ages of 50 to 69. Moreover, data on the frequencies and cost of further investigations and treatments were obtained based on women who attended the Ottawa Hospital during the years 2011 and 2012 and who were at average risk of developing breast cancer.

Some data were specific to genetic mutation carriers such as: data on the annual incidence of breast cancer, tumour histology (ER, HER2 status) and nodal status

(positive, negative). Accordingly, we assumed that the data belong to BRCA2 women are similar for the other high-risk women group because they have similar tumour progression rates according to evidences from the literature (Tilanus-Linthorst et al., 2007).

It was assumed that the interval cancers will be detected before the next screening cycle. This assumption was made based on the rapid progression rate among high risk women. In addition, it was assumed that the percentage of women who choose mastectomy is similar for women with screening detected cancers and for women with interval cancers.

For simplicity, we assumed that a mastectomy eliminates the risk of developing breast cancer while, according to the literature, mastectomy could lead to a greater than 90% reduction of the risk of breast-cancer development.

In reality, not all of the 10% of the women who developed breast cancer choose breast mastectomy (according to E. Warner, personal communication, October 12, 2012); some of these women choose lumpectomy followed by radiation (J. Seely, personal communication, June 10, 2014). Since no data were found in the literature on the percentage of women who choose lumpectomy and radiation, we assumed that all of the 10% of women who develop breast cancer choose to undergo mastectomy and breast reconstruction.

In our univariate analysis, we anticipated that the rate of women at high risk who choose to undergo mastectomy will increase due to increasing awareness among these women. However, if the addition of MRI proves to significantly increase the breast cancer detection and survival rate it is possible that women may choose regular MRI and mammography screening over losing their breast permanently – particularly women with

a slower progression rate (i.e., BRAC2 and other high-risk women). This might increase the cost-effectiveness of adding MRI (Pelvritis et al., 2006).

The cost of breast surgery could not be considered in this study as a treatment cost because of the data limitations. However, it is recommended that this cost be included in future studies when these data become available because it is an important treatment intervention.

One of the most important factors that was not considered in our study and that may have an impact on the effectiveness of adding MRI is the participation rate. This is of concern because the high rate of false-positive results produced by MRI screening may negatively affect women's commitment to regular screening.

Since one of the screening scenarios considered in the simulation is both MRI and mammography combined and since there was no data available on the sensitivity of digital mammography combined with MRI, our simulation model was conducted based on the sensitivity of film mammography.

Changes to the screening policy, in terms of either the screening interval or the age of the cohort that is offered the screening, were not considered in our study, though it might be worthwhile to determine whether these factors have an effect on the cost-effectiveness of adding MRI.

The TNM tumour size classification could not be used because we were limited by the availability of the data published in the literature on the tumour size of screening detected cancers, survival rates and interval cancers. However, if better data become available in the future, it would be more accurate to consider the TNM classification.

The improvement of breast-cancer treatment might undermine the cost-effectiveness of adding MRI since the major impact of MRI is early detection, which accordingly increases the survival rate. If the treatment progresses to the point where early detection is no longer important, then MRI would cease to be a cost-effective intervention.

Lastly, even though it might be important to evaluate the impact of breast-cancer screening, diagnosis, treatment and survivorship on the quality of life of high-risk women, it was not feasible to conduct a cost-utility study because of the lack of comprehensive data on utility values. More specifically, almost no study has considered the disutility associated with experiencing breast-cancer treatment, which is considered to be an important factor in determining the impact of early detection on women's quality of life since early-stage tumours do not require chemotherapy. Furthermore, some evidence suggests that the current quality of life measures are not accurate specifically to cancers. (Garau et al., 2011). Moreover, in our simulation, we assumed that the women who developed breast cancer either will be dead or will be cured after one year of treatment and restart screening. Accordingly, it is not worthwhile to consider the QALYs. Therefore, we chose a reasonable outcome measure, which is life years gained, that reflects the interest of the health-care system.

7. CONCLUSION

The study results suggested that the addition of MRI plays an important role in improving the screening of high-risk women in terms of increasing life years gained compared to receiving mammography screening only. Despite gaps in the published data from previous studies, our model gives the best possible estimation of the cost-effectiveness of the addition of MRI based on currently available data.

To our knowledge this is the first full cost-effectiveness evaluation of the addition of MRI to mammography for the screening of high-risk women that has been conducted in

Canada. The results of this study support the recommendations of the Cancer Care Ontario and the Ontario Health Technology Advisory Committee guidelines for expanding the Ontario Screening Program to integrate MRI with mammography screening for high-risk women aged 30 to 69 years (Ministry of Health and Long-Term Care, 2009).

Further research is recommended to include the social perspective and the direct costs that could not be considered in this study in order to overcome the limitations of this study and estimate whether the availability of better data in the future may alter the current results of our simulation. Additionally, it is recommended that the costs of lumpectomy plus radiation and breast surgery be included as treatment interventions in future studies when these data become available in order to give more accurate estimations of the cost-effectiveness of the addition of MRI.

Moreover, the consideration of utilities in a comprehensive manner by using appropriate measures of quality of life distributed among samples of Canadian high risk women who participated in the OBSP could be a useful addition to the economic evaluation of adding MRI to mammography. This is because early detection may contribute in raising high-risk women's quality of life in comparison with receiving treatment, even though the rapid and continuous improvement of treatment increases the survival rates regardless of the stage of breast cancer at the time of detection.

Given the fact that it is unlikely that a definitive randomized controlled trial will be performed, the results obtained from a range of models may provide useful contributions to the developing consensus relating to the long-term cost-effectiveness and clinical-effectiveness of screening for breast cancer through a combination of MRI and mammography (Lee et al., 2010).

8. REFERENCES

Afonso, N. (2009). Women at high risk for breast cancer – What the primary care provider needs to know. *Journal of the American Board of Family Medicine, 22*(1), 43-50. Retrieved from http://www.jabfm.org/content/22/1/43.full#cited-by

Ahern, C.H. (2008). *Statistical modeling in the optimization of breast cancer screening schedules* (unpublished doctoral thesis). Houston, TX: Rice University. Retrieved from http://scholarship.rice.edu/bitstream/handle/1911/61760/3362122.PDF?sequence=1

Antoniou, A., Pharoah, P.D.P., Narod, S. et al. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. *American Journal of Human Genetics, 72,* 1117-1130. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180265/pdf/AJHGv72p1117.pdf

Bougie, O., & Weberpals, J.I. (2011). Clinical considerations of BRCA1- and BRCA2-mutation carriers: A review. *International Journal of Surgical Oncology, vol. 2011*. Retrieved from http://www.hindawi.com/journals/ijso/2011/374012/#B52

Brekelmans, C.T.M., Seynaeve, C., Bartels, C.C.M., Tilanus-Linthorst, M.M.A., Meijers-Heijboer, E.J., Crepin, C.M.G., et al. (2001). Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *Journal of Clinical Oncology, 19*(4), 924-930.

Brown, M.L. (1992). Sensitivity analysis in the cost-effectiveness of breast cancer screening. *Cancer, 69*(S17), 1963-1967.

Canadian Agency for Drugs and Technologies in Health (CADTH). (2006). *Guidelines for the economic evaluation of health technologies (3rd ed.)*. Ottawa: CADITH.

Canadian Breast Cancer Foundation. (n.d.). *Staging and grading breast cancer*. Retrieved from http://www.cbcf.org/central/AboutBreastCancerMain/Diagnosis/Pages/StagingGrading.aspx

Canadian Cancer Society. (n.d.). *Triple negative and basal-like breast cancers*. Retrieved from http://www.cancer.ca/en/cancer-information/cancer-type/breast/pathology-and-staging/malignant-tumours/triple-negative-breast-cancer/?region=on

Canadian Cancer Society. (n.d.). *Risk factors for breast cancer*. Retrieved from http://www.cancer.ca/en/cancer-information/cancer-type/breast/risks/?region=bc, http://jabfm.org/content/22/1/43.full

Canadian Cancer Society. (2007). *Canadian cancer statistics 2007*. Toronto, ON: Canadian Cancer Society.

Canadian Cancer Society. (2009). *Canadian cancer statistics 2009*. Toronto, ON: Canadian Cancer Society.

Canadian Cancer Society. (2010). *Staging and grading for breast cancer*. Retrieved from http://www.cancer.ca/Canadawide/About%20cancer/Types%20of%20cancer/Staging%20and%20grading%20for%20breast%20cancer.aspx?sc_lang=en

Canadian Cancer Society. (2011). *Canadian cancer encyclopedia: Breast cancer overview*. Retrieved from http://info.cancer.ca/cceecc/default.aspx?Lang=E&toc=10#Early_detection

Canadian Cancer Society. (2012). *Canadian cancer statistics 2012*. Toronto, ON: Canadian Cancer Society.

Canadian Cancer Society. (2013). *Canadian cancer statistics 2013*. Toronto, ON: Canadian Cancer Society. Retrieved from http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/canadian-cancer-statistics-2013-EN.pdf

Canadian Cancer Society. (2014). *Canadian cancer statistics 2014*. Toronto, ON: Canadian Cancer Society. Retrieved from http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2014-EN.pdf

CancerLink. (n.d.). *Principles of cancer screening*. Retrieved from http://cancerlink.ru/enprinciples-cancer-screening.html

Caro, J.J., Möller, J., & Getsios, D. (2010). Discrete event simulation: The preferred technique for health-economic evaluations? *Value in Health, 13*(8), 1056-1060.

Carter, C.L., Allen, C., & Henson, D. (1989). Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer, 63*(1), 181-187.

Dos Santos Silva, I. (1999). *Cancer epidemiology: Principles and methods*. Lyon, France: International Agency for Research on Cancer. Retrieved from http://w2.iarc.fr/en/publications/pdfs-online/epi/cancerepi/

Dunfield, L., & Severn, M. (2007). *Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer [Technology report number 93]*. Ottawa: Canadian Agency for Drugs and Technologies in Health.

Enriquez, L., & Linitsky, J. (2009). Role of MRI in breast cancer management. *Cleveland Clinic Journal of Medicine, 76*(9), 525-532. Retrieved from http://www.ccjm.org/content/76/9/525.full

Fracheboud, J., de Koning, H.J., Beemsterboer, P.M.M., Boer, R., Verbeek, A.L.M., Hendriks, J.H.C.L., van Ineveld, B.M., Broeders, M.J.M., de Bruyn, A.E., & van der Maas, P.J. (1999). Interval cancers and breast screening in The Netherlands. *British Journal of Cancer, 81*(5), 912-917. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2374303/pdf/81-6690786a.pdf

Garau, M., Shah, K.K., Mason, A.R., Wang, Q., Towse, A., & Drummond, M.F. (2011). Using QALYs in cancer. *PharmacoEconomics, 29*(8), 673-685.

Gareth, E.D., Nisha, K., Yit, L., et al. (2014). MRI breast screening in high-risk women: Cancer detection and survival analysis. *Breast Cancer Research and Treatment* (electronic publication ahead of print).

Gloekler Ries, L.A., & Eisner, M.P. (n.d.). *Cancer of the female breast*. Bethesda, MD: National Cancer Institute. Retrieved from http://s3.amazonaws.com/zanran_storage/www.seer.cancer.gov/ContentPages/2471932313.pdf

Grebisch, I., Brown, J., Boggis, C., et al. (2006). Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs x-ray mammography of women at highfamilial risk of breast cancer. *British Journal of Cancer, 95*(7), 801-810. Retrieved from http://www.nature.com/bjc/journal/v95/n7/full/6603356a.html

Health Quality Ontario. (2010). *Cancer screening with digital mammography for women at average risk for breast cancer, magnetic resonance imaging (MRI) for women at high risk*. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377503/

Hartman, A.R., Daniel, B.L., Kurlan, A.W., Mills, M.A., Nowels, K.W., Dirbas, F.M., et al. (2004). Breast magnetic resonance image screening and ductal lavage in women at high genetic risk for breast carcinoma. *Cancer, 100*(3), 479-489.

Institute for Quality and Efficiency in Health Care. (2009). *Working paper modeling*. Retrieved from https://www.iqwig.de/download/Working_Paper_Modelling.pdf

Isaacs, C., Skates, S.J., Lehman, C., Marcom, K., Bowen, D.J., Domcheck, S., et al. (2004). Mammographic, MRI, and ultrasound characteristics of BRCA1, BRCA2, and other genetically high-risk women enrolled in a prospective multi-institution breast cancer screening trial [abstract]. *Journal of Clinical Oncology, 22*(14 Suppl), A9588.

Karnon, J., Stahl, J., Brennan, A., Caro, J.J., Mar, J., & Möller, J. (2012). Modeling using discrete event simulation : A report of the ISPOR-SMDM modeling good research practices task force – 4. *Value in Health, 15*, 821-827.

Kriege, M., Brekelmans, C.T.M., Boetes, C., Besnard, P.E., Zonderland, H.M., Objeijn, I.M., et al. (2004). Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *New England Journal of Medicine, 351*(5), 427-437.

Kuhl, C.K., Schrading, S., Leutner, C.C., Morakkabati-Spitz, N., Wardelmann, E., Fimmers, R., Kuhn, W., & Schild, H.H. (2005). Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *Journal of Clinical Oncology, 23*(33), 8469-8476.

Kurian, A.W., Daniel, B.L., Nowels, K.W., Ford, J.M., Plevritis, S.K., Kingham, K.E., et al. (2004). A pilot breast cancer screening trial for women at high inherited risk using clinical breast exam, mammography, breast magnetic resonance imaging, and ductal lavage: updated results after median follow-up of fourteen months. *Breast Cancer Research and Treatment, 88*(Suppl 1), A5013.

Lehman, C., Blume, J.D., Weatherall, P., Thickman, D., Hylton, N., Warner, E., et al. (2005). Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer,103*(9), 1898-1905.

Lehman, C., Gatsonis, C., Isaacs, C., Pisano, E., Ascher, S., Weatherall, P., et al. (2004). Cancer yield of mammography, MRI, and ultrasound in high-risk women enrolled in a prospective multi-institution breast cancer screening trial [abstract]. *Journal of Clinical Oncology, 22*(14 Suppl), A9626.

MARIBS Study Group. (2006). Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet, 365*(9473), 1769-1778.

Medical Advisory Secretariat. (2010). Cancer screening with digital mammography for women at average risk for breast cancer, magnetic resonance imaging (MRI) for women at high risk: an evidence-based analysis. *Ontario Health Technology Assessment Series, 10*(3), 1-55. Retrieved from http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_breast_cancer_screening_20100316.pdf

Menn, P., & Holle, R. (2009). Comparing three software tools for implementing Markov models for health economic evaluations. *Pharmacoeconomics, 27*(9), 745.753. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4733.2010.00775.x/pdf

Michaelson, J.S., Silverstein, M., Sgroi, D., Chiongsiatmoy, J.A., Taghian, A., Powell. S., Hughes, K., Comegno, A., Tamabe, K.K.,, & Smith, B. (2003). The effect of tumor size and lymph node status on breast carcinoma lethality. *Cancer, 98*(10), 2133-2143.

Ministry of Health and Long-Term Care. (2008). *Breast cancer screening*. Retrieved from http://www.health.gov.on.ca/en/public/programs/breastcancer/about.aspx

Ministry of Health and Long-Term Care. (2009). *Info bulletin #10016*. Retrieved from http://www.health.gov.on.ca/english/providers/program/ohip/bulletins/10000/bul10016.pdf

Ministry of Health and Long-Term Care. (2013). *OHIP schedule and benefits, 2013 – Integumentary system surgical procedures*. Retrieved from http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/m_skinbr.pdf

Moore, S.G., Shenoy, P.J., Fanucchi, L., Tumeh, J.W., & Flowers, C.R. (2009). Cost effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. *BMC Health Services Research*, *9*(9).

National Breast Cancer Center. (2006). *Magnetic resonance imaging for the early detection of breast cancer in women at high risk: a systematic review of the evidenc*e. Camperdown, New South Wales: NBCC.

National Cancer Institute. (n.d.a). *BRCA1 and BRCA2: Cancer risk and genetic screening*. Retrieved from http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA

National Cancer Institute. (n.d.b). *Surveillance, epidemiology and end results program*. Retrieved from http://seer.cancer.gov/about/

National Cancer Institute. (n.d.c). *General information about breast cancer*. Retrieved from http://www.cancer.gov/cancertopics/pdq/treatment/breast/Patient/page1

National Cancer Institute. (n.d.d). *Hormone therapy for breast cancer*. Retrieved from http://www.cancer.gov/cancertopics/factsheet/Therapy/hormone-therapy-breast

National Cancer Institute. (n.d.e). *Definition: invasive cancer*. Retrieved from http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45741

National Cancer Institute. (2006). *Preventive mastectomy*. Retrieved from http://www.cancer.gov/cancertopics/factsheet/Therapy/preventive-mastectomy

National Cancer Institute of Canada. (2006). *Canadian Cancer Statistics, 2006*. Toronto, ON: NCIC.

Nathanson, K.L., Schnall, M., & Domchek, S.M. (2009). Prospective study of breast MRI in BRCA1 and BRCA2 mutation carriers: effect of mutation status on cancer incidence. *Breast Cancer Research and Treatment, 118,* 539-546.

Norman, R.P.A., Evans, D.G., Easton, D.F., & Young K.C. (2007). The cost-utility of magnetic resonance imaging for breast cancer in BRCA1 mutation carriers aged 30-49. *European Journal of Health Economics, 8*(2),137-144.

Ottawa Public Health. (2012). *Morbidity and mortality in Ottawa, 2012*. Ottawa, ON: City of Ottawa.

Parsonage, M., & Neuberger H. Discounting of health benefits. *Health Economics, 1*(1), 71-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1342633

Plevritis, S.K., Kurian, A.W., Sigal, B.M., Daniel, B.L., Ikeda, D.M., Stockdale, F.E., et al. (2006). Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA, 295*(20), 2374-2384.

Pisano, E.D., Gatsonis, C., Hendrick, E., Yaffe, M., Baum, J.K., Acharyya, S., Conant, E.F., Fajardo, L.L., Bassett, L., D'Orsi, C., Jong, R., & Rebner, M. (2005). Diagnostic performance of digital versus film mammography for breast-cancer screening. *New England Journal of Medicine, 353*(17), 1773-1783.

Podo, F., Sardanelli, F., Canese, R., D'Agnolo, G., Natali, P.G., Crecco, M., et al. (2002). The Italian multicenter project on evaluation of MRI and other imaging modalities in early detection of breast cancer in subjects at high genetic risk. *Journal of Experimental and Clinical Cancer Research, 21*(3 Suppl), 115-124.

Public Health Agency of Canada. (2006). *Organized breast cancer screening programs in Canada: report on performance in 2005 and 2006*. Retrieved from http://www.phac-aspc.gc.ca/cd-mc/publications/cancer/obcsp-podcs05/pdf/breast-cancer-report-eng.pdf

Sardanelli, F., Corcione, S., Manoukian, S., Cortesi, L., Di Maggio, C., & Podo, F. (2004). Mutlicenter screening of 235 women at genetic and/or familial high risk of breast cancer: mammography, ultrasound, and MR [abstract]. *Radiological Society of North America Scientific Assembly and Annual Meeting Program* (SST01-05).

Scheuer, L., Kauff, N., Robson, M., Kelly, B., Barakat, R., Satagopan, J., et al. (2002). Outcome of preventive surgery and screening for breast and ovarian cancer in *BRCA* mutation carriers. *Journal of Clinical Oncology, 20*(5), 1260-1268.

Spiegel, T.N., Esplen, M.J., Hill, K.A., Wong, J., Causer, P.A., & Warner, E. (2011). Psychological impact of recall on women with BRCA mutations undergoing MRI surveillance. *The Breast, 20*(5), 424-430. Retrieved from http://www.thebreastonline.com/article/S0960-9776%2811%2900094-4/abstract?source=aemf

Silverstein, M.J. (1998). Ductal carcinoma in situ of the breast: Controversial issues. *The Oncologist, 3*(2), 94-103.

Statistics Canada. (2011). *Leading causes of death in Canada, 2008*. Ottawa, ON: Statistics Canada.

Statistics Canada. (2011). *Study: Trends in the prevalence of cancer, 1997-2008*. Retrieved from http://www.statcan.gc.ca/daily-quotidien/120118/dq120118a-eng.htm

Taneja, C., Edelsberg, J., Weycker, D., et al. (2009). Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. *Journal of the American College of Radiology, 6*, 171-179.

The Ottawa Hospital. (n.d.). *Ontario breast screening program*. Retrieved from http://www.ottawahospital.on.ca/wps/portal/Base/TheHospital/ClinicalServices/DeptPgrmCS/Programs/CancerProgram/AboutTheCancerProgram/OurProgramsClinics/OntarioBreastScreeningPrgm

Tilanus-Linthorst, M.M.A., Obdeijn, I-M., Hop, W.C.J., Causer, P.A., Leach, M.O., Warner, E., Pointon, L., Hill, K., Klijn, J.G.M., Warren, R.M.L., & Gilbert, F.J. (2007). A BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, UK, and Canadian MRI screening trials. *Clinical Cancer Research, 13*(24), 7357-7362 Retrieved from http://clincancerres.aacrjournals.org/content/13/24/7357.full.pdf+html

TNM Classification Help. (2005). *Manual for cancer staging – Breast tumours*. Retrieved from http://cancerstaging.blogspot.ca/2005/02/breast-tumours.html

Treasury Board of Canada Secretariat. (2007). *Canadian cost-benefit guide: Regulatory proposals*. Ottawa, ON: Treasury Board of Canada Secretariat.

Vasen, H.F.A., Tesfay, E., Bonnstra, H., Mourits, M.J.E., Rutgers, E., Verheyen, R., et al. (2005). Early detection of breast and ovarian cancer in families with BRCA mutations. *European Journal of Cancer, 41*, 549-554.

Villanti, A.C., Jiang, Y., Abrams, D.B., & Pyenson, B.S. (2013). A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PLoS ONE, 8*(8). Retrieved from http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0071379&representation=PDF

Warner, E., Causer, P., Hill, K., et al. (2005). MRI surveillance downstages invasive cancer (IC) to DCIS in women at high risk for hereditary breast cancer. Proceedings of the 28th Annual San Antonio Breast Cancer Symposium. *Breast Cancer Res Treat, 94*(suppl 1), S2505.

Warner, E., Messersmith, H., Causer, P., Eisen, A., Shumak, R., & Plewes, D. (2008). Systematic review: Using magnetic resonance imaging to screen women at high risk for breast cancer. *Annals of Internal Medicine, 148*(9), 671-679. Retrieved from http://annals.org/article.aspx?articleid=740814

Warner, E., Messersmith, H., Causer, P., Eisen, A., Shumak, R., & Plewes, D. (2012). Magnetic resonance imaging screening of women at high risk for breast cancer.

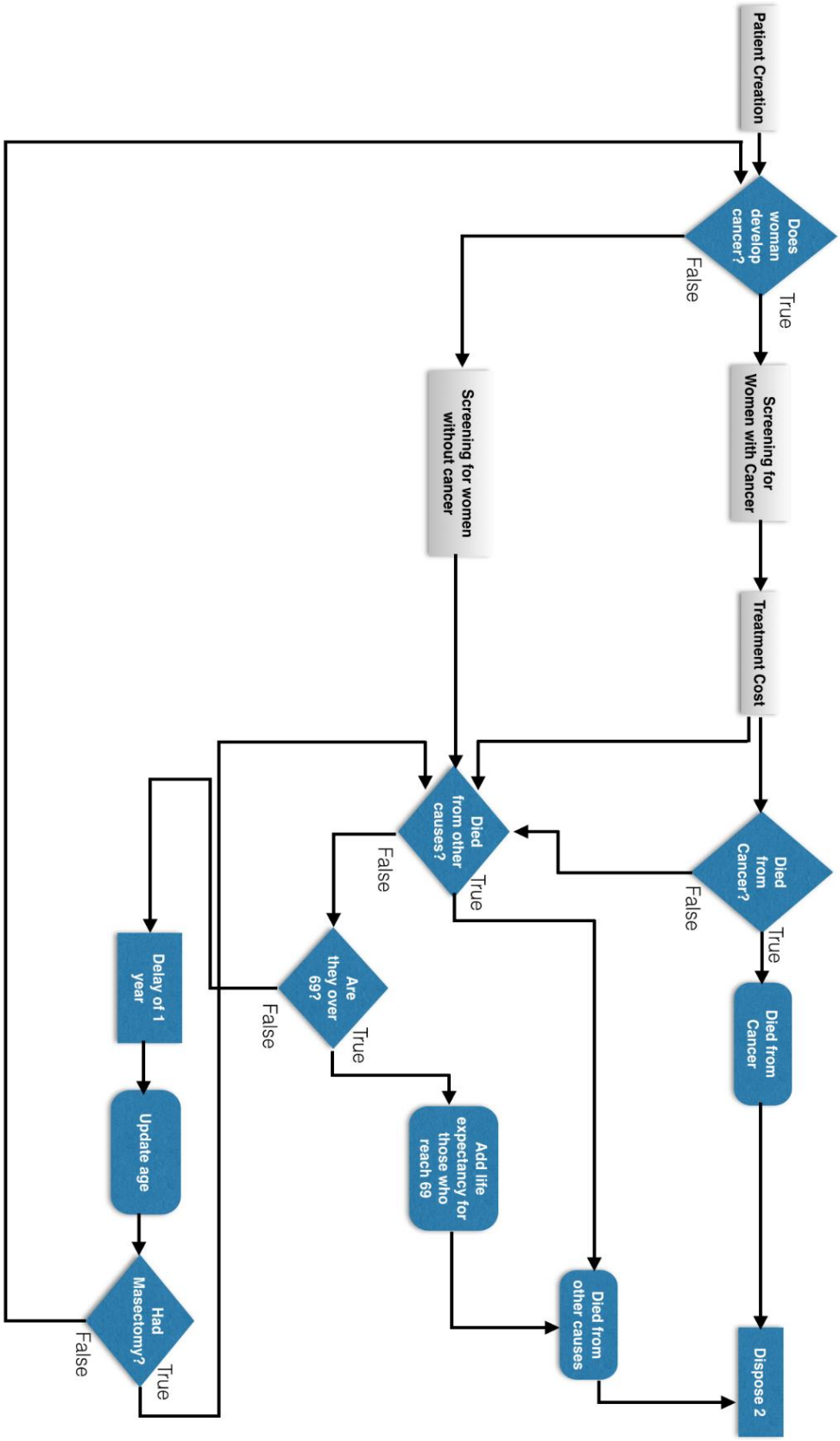
Program in evidence-based Care: Evidence-based guideline no. 15-11, version 2. Toronto, ON: Cancer Care Ontario.

Warner, E., Plewes, D.B., Hill, K.A., Causer, P.A., Zubovits, J.T., Jong, R.A., et al. (2004). Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA, 292*(11), 1317-1325.

Weinstein, M.C. (2008). How much are Americans willing to pay for a quality-adjusted life year? *Medical Care, 46*(4), 343-345. Retrieved from http://www.medicine.mcgill.ca/epidemiology/courses/EPIB654/Summer2010/Policy/Weinsten%20cost%20per%20QALY%20threshold%20Med%20Care.pdf

Weinstein, S., Localio, A.R., Conant, E.F., Rosen, R., Thomas, K.M., & Schnall, K.M. (2009). Multimodality screening of high-risk women. *Journal of Clinical Oncology, 27*(36), 6124-6128.

APPENDIX A: THE DISCRETE-EVENT SIMULTION MODEL FRAMEWORK



APPENDIX B: SIMULTION MODEL INPUT PARAMETERS

Table B-1: Distributions of BRCA1, BRCA2 and other high risk groups

Risk Type	No. of Women Screened	Probability of Risk Type
BRCA1	18	7.41%
BRCA2	40	16.46%
Other	185	76.13%

Source: Hampton Park Plaza screening centre based on a sample of 243 high-risk women who attended the centre during the years 2011 and 2012

Table B-2: Annual incidence rates of breast cancer among the three high-risk groups per age

Age Group	BRCA1	BRCA2	Other High-Risk (assumed)
30-34 years	0.74	0.36	0.36
35-39 years	1.59	0.78	0.78
40-44 years	2.92	0.91	0.91
45-49 years	4.28	1.34	1.34
50-54 years	2.65	1.76	1.76
55-59 years	3.01	2	2
60-64 years	2.7	2.17	2.17
65-69 years	2.96	2.38	2.38

Source: Antoniou et al., 2003

Table B-3: Sensitivity, specificity, and false positive rate of screening strategies

	MRI	Mammography	MRI and Mammography	Ultrasound*
Sensitivity	80%	36.80%	87.40%	17%
Specificity	97%	97.10%	94.20%	88%
False positive	3%	2.90%	5.80%	12%

Sources: Warner et al., 2012 (meta-analysis)

* Weinstein et al., 2009

Table B-4: Distribution of cancer-detected by screening and interval cancers per tumor size

Screening Strategy	DCIS	≤ 10 mm (Small)	11_20 mm (Medium)	> 20 mm (Large)
Mammography	49.1%	40.9%	8.2%	1.7%
MRI	10.0%	46.7%	30.0%	13.3%
Both	21.4%	28.6%	35.7%	14.3%
Interval*	2.1%	12.2%	43.9%	41.7%

Source: Warner et al., 2004; MARIBS Study Group, 2006; Scheuer et al., 2002

* Fracheboud et al., 1999

Table B-5: Frequencies and probabilities of receiving biopsies

Further Investigations	Frequency	Probability of Receiving Test
Ultrasound biopsy	712	34.69%
Stereotactic biopsy	222	10.80%
MRI biopsy	1118	54.48%

Source: Ottawa Hospital

Table B-6: Costs of screening and further investigations

Screening and Further investigations	Cost (CAN$)
MRI	617.45
Mammography	91.27
Mammography cost= additional diagnostic mammography+ mammography screening	203.97
Diagnostic mammography	112.70
MRI and mammography combined	708.72
Ultrasound	102.10
Ultrasound biopsy	325.57
Stereotactic biopsy	1,010.94
MRI biopsy	1,638.09

Source: Ottawa Hospital

Table B-7: The distribution of ER, PR, and HER2 receptors per the three risk groups

Tumor Histology	BRCA1 (n=23)	BRCA2 (n=14)	Other High-Risk (assumed)
ER-positive	8 (35%)	12 (86%)	12 (86%)
PR-positive	5 (22%)	10 (71%)	10 (71%)
HER2-positive	1 (4%)	1 (7%)	1 (7%)

Source: Passaperuma et al., 2012

Table B-8: Distribution of nodal involvement per screening strategy, risk groups and interval cancers

	Mammography	MRI*
BRCA ½	41%	19%
Other high risk	18%	12%
Interval	62%	28%

* It was assumed that the nodal involvement per both screening combined is equal to the nodal involvement per MRI alone screening

Source: Taneja et al., 2009

Table B-9: Mastectomy and breast reconstruction costs

Code	Description	Costs (CAN$)
Mastectomy cost:		
R109	Mastectomy, radical or modified radical (with or without biopsy)	685.0
Breast reconstruction:		
R119	Breast mound creation by prosthesis as sole procedure	350.0
R118	Breast skin reconstruction by local flaps or grafts, includes Wise pattern skin flaps and de-epithelialized skin flaps	405.6
R156	Breast mound creation by insertion of tissue expander, includes creation of submuscular pocket	425.0
R114	Revision of breast mound	230.3
R120	Nipple-areola reconstruction by grafts and/or flaps	300.0
R142	Nipple-areola tattooing – unilateral	175.0
R143	Contralateral balancing mastopexy or reduction, to include nipple transplantation or grafting, if rendered	472.2
R144	Contralateral balancing augmentation mammoplasty	350.0
Total cost of mastectomy with reconstruction		3,393

Source: Ministry of Health and Long-Term Care, 2013

Table B-10: Treatment costs per ER. HER2 and nodal status

Breast Cancer Type	Treatments Costs (CAN$)
ER status HER2 nodal negative	1,560.6
ER status positive HER2 nodal negative	1,560.6
ER status nodal negative HER2 positive	48,560.6
ER status HER2 positive nodal negative	48,560.6
ER status HER2 negative nodal positive	1,560.6

ER status nodal positive HER2 negative	1,657.5
ER status negative HER2 nodal positive	54,057.5
ER status HER2 nodal positive	54,057.5

Source: Ottawa Hospital

Table B-11: Death from all causes per age

Age Group	Female Rate (2003-2007)	Female Deaths (2003-2007)
20 to 34 years	23.8	0.0%
35 to 39 years	59.1	0.1%
40 to 44 years	100.2	0.1%
45 to 49 years	155.4	0.2%
50 to 54 years	247.5	0.2%
55 to 59 years	374.7	0.4%
60 to 64 years	587.9	0.6%
65 to 69 years	921.9	0.9%
70 to 74 years	1580.9	1.6%
75 to 79 years	2791.1	2.8%
80 to 84 years	4888.4	4.9%
85 to 89 years	8849.1	8.8%
90 + years	18307.8	18.3%

*Total population= 100,000

Source: Ottawa Public Health, 2012

Table B-12: Death from breast cancer per tumor size and nodal status

Tumor Size	Node Negative	Node Positive
DCIS*	0	0
≤ 10 mm (Small)	0.00	6.97
11_20 mm (Medium)	0.00	8.98
> 20 mm (Large)	6.86	26.56

Source: Gloekler Ries & Eisner, n.d. (the SEER database)

*Silverstein, 1998

APPENDIX C: SIMULATION MODEL KEY PARAMETERS VARIATIONS THAT CONSIDERED IN THE UNIVARIATE SENSETIVITY ANALYSIS

Table C-1: Distribution of tumor size at time of detection by both screening strategies combined*

Assumptions	DCIS	≤ 10 mm (Small)	11_20 mm (Medium)	>20 mm (Large)
5% of the tumours from each tumour size classification are detected one stage earlier	23.3%	40.2%	25.9%	10.5%
10% of the tumours from each tumour size classification are detected one stage earlier	25.4%	39.5%	25.1%	10.0%
20% of the tumours from each tumour size classification are detected one stage earlier	29.5%	38.1%	23.6%	8.9%

* The tumour size distribution at the time of detection by mammography screening alone stayed the same as in the base-case scenario

Source: Based on data that were obtained and combined from three studies (Warner et al., 2004; MARIBS Study Group, 2006; Scheuer et al., 2002)

Table C-2: Screening and further investigations costs

Screening and Further Investigations	Base-Case Costs (CAN$)	Cost Increased by 20% (CAN$)	Cost decreased by 20% (CAN$)
MRI	617.5	740.9	494.0
Mammography	91.3	109.5	73.0
Mammography cost= additional diagnostic mammography+ mammography screening	204.0	244.8	163.2

Diagnostic mammography	112.7	135.2	90.2
MRI and mammography combined	708.7	850.5	567.0
Ultrasound	102.1	122.5	81.7
Ultrasound biopsy	325.6	390.7	260.5
Stereotactic biopsy	1010.9	1213.1	808.8
MRI biopsy	1638.1	1965.7	1310.5

Source: Ottawa Hospital

Table C-3: Breast cancer treatments costs

Breast Cancer Types	Base-Case Costs (CAN$)	Cost Increased by 20% (CAN$)	Cost decreased by 20% (CAN$)
ER status HER2 nodal negative	1560.6	1872.7	1248.5
ER status positive HER2 nodal negative	1560.6	1872.7	1248.5
ER status nodal negative HER2 positive	48560.6	58272.7	38848.5
ER status HER2 positive nodal negative	48560.6	58272.7	38848.5
ER status HER2 negative nodal positive	1560.6	1872.7	1248.5
ER status nodal positive HER2 negative	1657.5	1989.0	1326.0
ER status negative HER2 nodal positive	54057.5	64869.0	43246.0
ER status HER2 nodal positive	54057.5	64869.0	43246.0
Mastectomy	3393.1	4071.7	2714.4

Source: Based on data obtained from the Ottawa Hospital and Ministry of Health and Long-Term Care, 2013

Table C-4: Type of high risk considered

Risk Type	No. of Women Screened*	Probability of Risk Type
BRCA1	18	31.03%
BRCA2	40	68.97%

*243 high-risk women attended the screening centre during the years 2011 and 2012, 58 of them are genetic mutations carriers

Source: Hampton Park Plaza screening centre

Table C-5: Breast cancer annual incidence

	Increased by 1 %			Increased by 2%		
Age Group	**BRCA1**	**BRCA2**	**Other**	**BRCA1**	**BRCA2**	**Other**
30-34 years	0.75	0.36	0.36	0.75	0.37	0.37
35-39 years	1.61	0.79	0.79	1.62	0.80	0.80
40-44 years	2.95	0.92	0.92	2.98	0.93	0.93
45-49 years	4.32	1.35	1.35	4.37	1.37	1.37
50-54 years	2.68	1.78	1.78	2.70	1.80	1.80
55-59 years	3.04	2.02	2.02	3.07	2.04	2.04
60-64 years	2.73	2.19	2.19	2.75	2.21	2.21
65-69 years	2.99	2.40	2.40	3.02	2.43	2.43

Source: Based on data from Antoniou et al., 2003

Table C-6: Nodal involvement distribution by risk type and interval cancers

	Increased by 25%		Increased by 50%	
Nodal Involvement	**Mammography**	**MRI**	**Mammography**	**MRI**
BRCA ½	0.51	0.24	0.62	0.29
Other High Risk	0.23	0.15	0.27	0.18
Interval	0.78	0.35	0.93	0.42

Source: Based on data from Lee et al., 201

Table C-7: Deaths from breast cancer by tumor size and node status

Tumor Size	Node Negative	Node Positive
DCIS	0.00	0.00
small decreased by 20%	0.00	5.58
medium decreased by 10%	0.00	8.08
large decreased by 5%	6.52	25.23

Source: Gloekler Ries & Eisner, n.d. (the SEER database)

Figure C-1: Univariate sensitivity analysis results

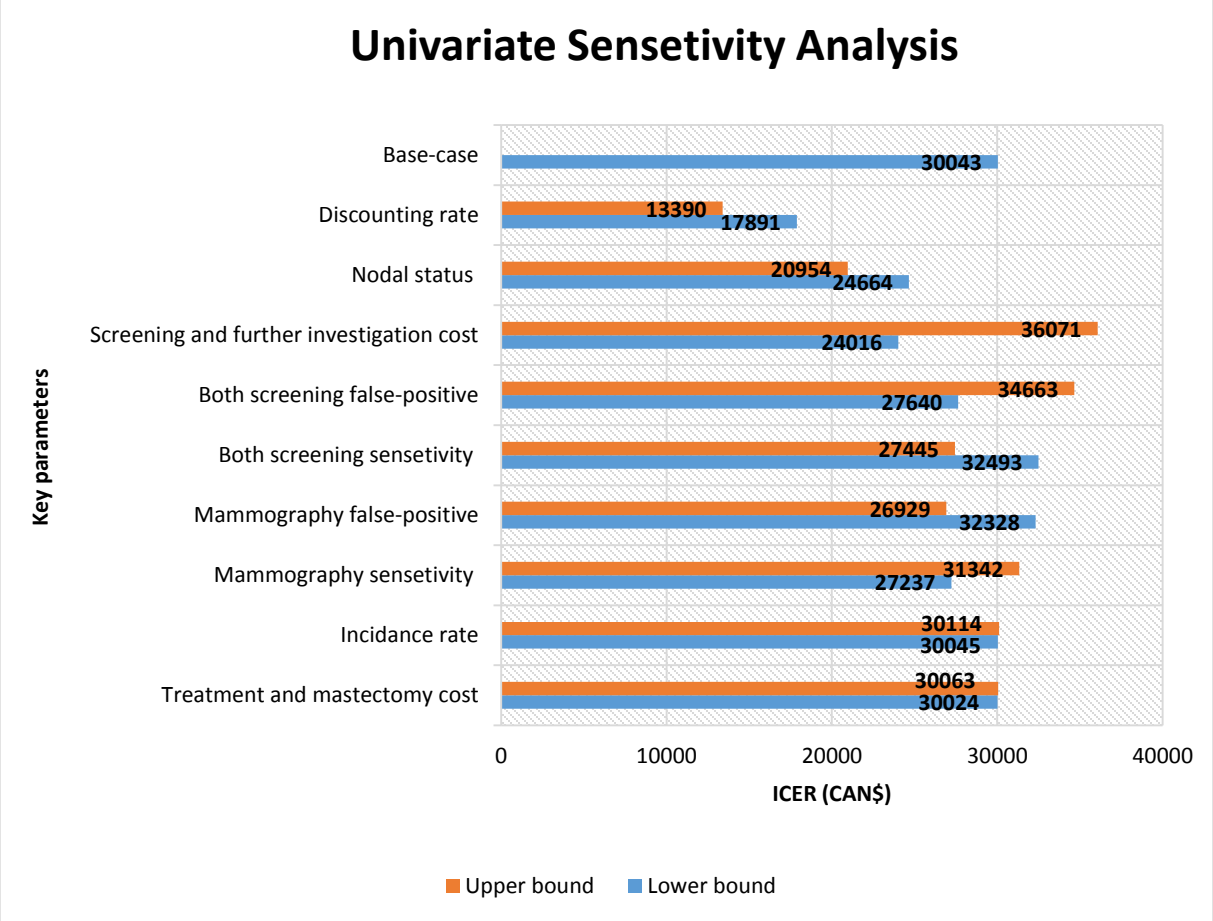


Figure C-2: Univariate sensitivity analysis results (Con.)