January 2019

Cost effectiveness of bilateral prophylactic mastectomy with and without different breast reconstruction techniques versus screening in women with high risk of breast cancer in the Canadian province of Ontario

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Graduate Program in Surgery

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Clinical Science

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Abstract

We aimed to investigate the cost-effectiveness of bilateral prophylactic mastectomy (BPM) with and without different reconstruction for the purpose of determining which strategies represent value for money. We developed a decision analytic model to project the lifetime clinical and economic consequences of different strategies. The decision model was parameterized using 10-year follow up and cost data from Ontario administrative health databases and Ontario Cancer registry. Compared to the organized screening-based strategy, surgical strategies ranged from being more effective and cost-saving and up to being associated with an incremental cost effectiveness ratio (ICER) of $63,010 per quality-adjusted life year (QALY) gained, with BPM with immediate one-stage acellular dermal matrix (ADM)-assisted implant breast reconstruction having the greatest incremental QALY of 1.157 and lowest ICER of $9,615. BPM with immediate one-stage ADM-assisted implant breast reconstruction is the most cost-effective strategy and appears to offer the highest value for money.
Keywords

Cost-Effectiveness, High breast cancer risk, Screening, Bilateral prophylactic mastectomy, Immediate breast reconstructions, ADM, Breast Cancer, Incremental Cost Effectiveness Ratio, Quality Adjusted Life Year.
Co-Authorship Statement

Badria Eid Al Johani designed the studies, performed the statistical analyses and drafted the manuscripts. Malek Hannouf, Aaron Grant, Chris Doherty, Gregory S. Zaric participated in the design of the studies and interpretation of the results. Muriel Brackstone participated in the design of the studies, participated in statistical analyses and drafting the manuscripts and supervised this work as part of Dr. AlJohani’s Masters of Surgery thesis.
Acknowledgments

I would like to express my special appreciation and thanks to my advisor Dr. Muriel Brackstone. You have been a tremendous mentor for me. I would like to thank you for encouraging my research and for allowing me to grow as a breast surgeon and as research scientist. Your advice in both research as well as in my career have been priceless. I would also like to thank my committee members, Prof. Gregory S. Zaric, Dr. Aaron Grant, Dr. Chris Doherty, for serving as my committee members even at hardship. I would especially like to thank Malek Bassem Hannouf and Cancer Registry of Cancer Care Ontario and Ontario Health for support in my master’s thesis.

A special thanks to my family. Words cannot express how grateful I am for all of the sacrifices that you have made on my behalf. Your support was what sustained me thus far. I would also like to thank all my friends who supported me in writing and incented me to strive towards my goal.
# Table of Contents

Abstract ................................................................................................................................. ii

Keywords ............................................................................................................................. iii

Co-Authorship Statement ....................................................................................................... iv

Acknowledgments ................................................................................................................ v

Table of Contents ................................................................................................................ vi

List of Tables ........................................................................................................................ xi

List of Figures ........................................................................................................................ xii

List of Appendices ................................................................................................................ xiii

List of Abbreviations ............................................................................................................ xiv

## Chapter 1 Introduction and Objectives

1.1 Breast cancer risk factors ............................................................................................... 1

1.2 Breast cancer screening in high-risk women ................................................................. 2

1.3 The need for this study .................................................................................................. 3

1.4 Objectives and research framework ............................................................................. 4

## Chapter 2 Literature review

2.1 Epidemiology of breast cancer ...................................................................................... 6

2.1.1 Tumor features ...................................................................................................... 6

2.1.2 Histological type .................................................................................................. 9

2.1.3 Molecular factors ................................................................................................. 9

2.1.4 Familial breast cancer ......................................................................................... 10

2.1.5 Epidemiology of breast cancer in Canada .......................................................... 12
2.2 High risk breast cancer ................................................................. 12
  2.2.1 Breast cancer Risk assessment models ........................................... 13
  2.2.2 Genetic counselling.......................................................................... 17
  2.2.3 Familial breast cancer risk ............................................................. 18
    2.2.3.1. BRCA1 and BRCA2 gene and Multi-gene panel ......................... 20
    2.2.3.2. Tumor characteristic in familial breast cancer ............................ 21
      2.2.3.2.1 Tumor characteristics of BRCA1-related breast cancer ............ 21
      2.2.3.2.2 Tumor characteristics of BRCA2-related breast cancer .......... 24
      2.2.3.2.3 Tumor characteristics of non-BRCA1- and non-BRCA2-related breast cancer ................................................................. 26
    2.2.3.3. Penetrance (low, moderate, and high) ..................................... 27
    2.2.3.4. Ashkenazi Jewish population risk .......................................... 27
    2.2.3.5 Male breast cancer .................................................................... 28
  2.3 Breast cancer screening ........................................................................ 30
    2.3.1 Breast cancer screening in Canada ................................................ 31
    2.3.2 Breast cancer screening potential harm .......................................... 33
    2.3.3 Participation in breast cancer screening .......................................... 35
    2.3.4 High risk Breast cancer screening .................................................. 36
  2.4 Breast cancer risk reduction techniques ................................................ 37
    2.4.1 Risk reduction mastectomy ........................................................... 37
      2.4.1.1 prophylactic mastectomy ......................................................... 42
      2.4.1.2 Breast cancer risk after prophylactic mastectomy ....................... 46
      2.4.1.3 Skin sparing prophylactic mastectomy ..................................... 49
5.3 Recommendations for future research ............................................ 139

5.4 Conclusion ...................................................................................... 140

5.5 Acknowledgment ........................................................................... 141

Bibliography .......................................................................................... 142

Curriculum Vitae .................................................................................... 187
List of Tables

Table 1. Patient characteristics of 17,793 Ontarian women identified at high risk of breast cancer during the period from January 1, 2005 to December 31, 2015 in Ontario by type of breast cancer risk management strategy undertaken………………. 107

Table 2. Patient characteristics of 3,428 matched1 women identified at high risk of breast cancer by type of breast cancer risk management strategy undertaken. …… 109

Table 3. Base case monthly probabilities and sources……………………………… 111

Table 4. Base case monthly cost estimates of healthcare services and sources by type of breast cancer risk management strategy and phase of care. ………………… 117

Table 5. Baseline life-time outcomes of the decision model………………………… 123
List of Figures

Figure 1  Acellular dermal matrix (ADM) .......................................................... 59

Figure 2. Acellular dermal matrix revascularized and incorporated into the recipient site… 60

Figure 3 Decision analytic model for women at high risk for breast cancer………………. 86

Figure 3a Breast cancer risk management decision ............................................... 86

Figure 3b Schematic representation of Markov model structure “A” ......................... 86

Figure 3c Schematic representation of Markov model structure “B” ......................... 87

Figure 3d Schematic representation of Markov model structure “C” ......................... 87

Figure 3f. Schematic representation of Markov model structure “D” ......................... 88

Figure 4 Differences in costs and effects between model strategies using a cost-effectiveness plane………………………………………………………………………….. 124
List of Appendices

Appendix A. Ethical Approval ......................................................... 186
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>Atypical ductal hyperplasia</td>
</tr>
<tr>
<td>ADM</td>
<td>Acellular dermal matrix</td>
</tr>
<tr>
<td>ALH</td>
<td>Atypical lobular hyperplasia</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia mutated</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BBD</td>
<td>Benign breast disease</td>
</tr>
<tr>
<td>BOADICEA</td>
<td>Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithms</td>
</tr>
<tr>
<td>BPM</td>
<td>Bilateral prophylactic mastectomy</td>
</tr>
<tr>
<td>BRCA</td>
<td>BReast CAncer gene</td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm</td>
</tr>
<tr>
<td>BRRM</td>
<td>Bilateral risk-reducing mastectomy</td>
</tr>
<tr>
<td>BRIP1</td>
<td>BRCA1 interacting protein C-terminal helicase 1</td>
</tr>
<tr>
<td>BSO</td>
<td>Bilateral Salpingo-Oophorectomy</td>
</tr>
<tr>
<td>CBE</td>
<td>Clinical breast examination</td>
</tr>
<tr>
<td>CCHS</td>
<td>Canadian Community Health Survey</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CCI</td>
<td>Canadian Classification of Health Intervention</td>
</tr>
<tr>
<td>CCRS</td>
<td>Continuing Care Reporting System</td>
</tr>
<tr>
<td>CPM</td>
<td>Contralateral prophylactic mastectomy</td>
</tr>
<tr>
<td>CRRM</td>
<td>Contralateral risk-reducing mastectomy</td>
</tr>
<tr>
<td>DAD</td>
<td>Discharge Abstract Database</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>DIEP</td>
<td>Deep inferior epigastric perforator</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen receptor</td>
</tr>
<tr>
<td>ERBB2</td>
<td>v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association studies</td>
</tr>
<tr>
<td>HCD</td>
<td>Home Care Database</td>
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<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IBIS</td>
<td>International Breast Cancer Intervention Study</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
</tr>
<tr>
<td>LAMBDA</td>
<td>Log odds of carrying an Ancestral Mutation in BRCA1 or BRCA2 for a Defined personal and family cancer history in an Ashkenazi Jewish</td>
</tr>
</tbody>
</table>
woman.

LCIS Lobular carcinoma in situ
MBC Male breast cancer
MRI Magnetic resonance imaging
NAC Nipple-areolar complex
NACRS National Ambulatory Care Reporting System
NCI National Cancer Institute
NDFP New Drug Funding Program
NRS National Rehabilitation Reporting System
NSQIP National Surgical Quality Improvement Program
NSM Nipple-sparing mastectomy
NST No special type
OBSP Ontario Breast Screening Program
OCR Ontario Cancer Registry
ODB Ontario Drug Benefit
OHCAS Ontario Home Care Administrative System
OHIP Ontario Health Insurance Plan
PALB2 Partner and localizer of BRCA2
PM Prophylactic mastectomy
PR Progesterone receptor
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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<td>QLI</td>
<td>Quality of Life Index</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RRM</td>
<td>Risk reduction mastectomy</td>
</tr>
<tr>
<td>RPDB</td>
<td>Registered Persons Database</td>
</tr>
<tr>
<td>SDS</td>
<td>Same Day Surgery</td>
</tr>
<tr>
<td>SSM</td>
<td>Skin-sparing mastectomy</td>
</tr>
<tr>
<td>STAR</td>
<td>Study of Tamoxifen and Raloxifene</td>
</tr>
<tr>
<td>TE</td>
<td>Tissue Expander</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumor-Node-Metastasis</td>
</tr>
<tr>
<td>TP53</td>
<td>tumor protein 53</td>
</tr>
<tr>
<td>TRAM</td>
<td>Transverse rectus abdominis myocutaneous</td>
</tr>
<tr>
<td>VUS</td>
<td>Variant of uncertain clinical significance</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction and Objectives

Worldwide, breast cancer is the most prevalent cancer and the second leading cause of cancer-related deaths among women. The International Agency for Research on Cancer (IARC) and GLOBOCAN reported in 2012, 1.67 million women were diagnosed with, and 522,000 women died from, breast cancer [1]. In Canada, 26,300 new cases were diagnosed in 2017; these cases represented 26% of all newly diagnosed cancers in women as reported by the Canadian Cancer Society [2]. Breast cancer incidence rates oscillated from 1988 to 2004, presumably due to population changes in hormone-associated factors such as age at menarche, gestation, menopause, breastfeeding, oral contraceptives and hormone replacement therapy use [3]. A familial history, especially in first-degree relatives, is a major risk factor for breast cancer development [4].

1.1 Breast cancer risk factors

The estimated general population lifetime risk of a breast cancer diagnosis in North America is 1 in 8. A wide array of factors is associated with an increased breast cancer risk, but age is the predominant risk factor. Nearly 80% of breast cancers are diagnosed in women ≥50 years of age, and the odds of a breast cancer diagnosis increases with increasing age [5], family history of hereditary breast cancer [6], having high-risk benign breast disease (e.g., atypical ductal hyperplasia, lobular carcinoma in situ [7,8], the presence of dense breasts in the mammogram image [9], early life exposure to ionizing radiation [10] and exposure to occupation-associated hazards during carcinogen handling, and exposure to endocrine disrupting chemicals [11] are additional factors associated with an increased risk of a breast cancer diagnosis.

Results of genetic studies using profiling technology indicate that the BReast CAncer gene 1 (BRCA1) and BReast CAncer gene 2 (BRCA2) genes are genetic risk factors
associated with a breast cancer diagnosis at a younger age [12,13]. These genes participate in some DNA repair pathways [14,15] and are associated with the development of hereditary breast cancer (approximately 30–70%) [16]. Results of genetic research studies indicate that the presence of germline mutations involving the BRCA1 or BRCA2 genes increases lifetime breast cancer risk to approximately 80% [17,16]. Over the past 20 years, BRCA1 and BRCA2 have been the primary focus of clinical genetic testing for hereditary breast cancer risk. These high-penetrance genes are responsible for Hereditary Breast and Ovarian Cancer Syndrome. Eric and colleagues [18] using US data indicated that most of patients who had negative test results for BRCA1 and BRCA2 rarely underwent additional testing. The patients who were tested further tended to be a small subset of individuals with distinctive personal or family histories, or both, suggestive of other high-penetrance hereditary cancer syndromes (e.g., associated with the genes CDH1 (hereditary diffuse gastric cancer syndrome), PTEN (PTEN hamartoma tumor syndrome), STK11 (Peutz-Jeghers syndrome), and TP53 (Li-Fraumeni syndrome) [18]. The genes ATM, CHEK2, and PALB2 are added to the above list for which there is sufficient evidence to recommend breast magnetic resonance imaging (MRI) and risk-reducing mastectomy [19].

1.2 Breast cancer screening in high-risk women

Since 1995, population and individual breast cancer risks have been assessed using validated statistical models. Models calibrated for accurate estimation of population risk are useful for cost-benefit analyses. However, risk assessment methods should also accurately assess individual risk so that valid prevention and treatment plans can be designed for individual patients [20].

The decision to refer a patient for testing and genetic counseling can be based on US Preventative Services Task Force guidelines [21]. Breast cancer screening of high-risk women is useful for early detection of breast cancer. Routine breast cancer screening for
a high-risk group includes mammographic imaging, breast ultrasound and MRI [22]. Mammography is the initial diagnostic tool used for breast cancer screening [23]. It is the standard of care for early detection of breast cancer. Mammography has a diagnostic sensitivity of 77–95% and a diagnostic specificity of 94–97% [24]. If screening mammogram results indicate the presence of any abnormal clinical characteristics, women who receive a mammography evaluation in the absence of clinical signs or symptoms will be referred for further investigation [25]. Ultrasound of the breast at the target site of interest may also be recommended because the diagnostic accuracy of mammography decreases as breast tissue density increases [25]. In most breast imaging practices, ultrasound is predominantly used as an adjunct to mammography. It is primarily used for problem-solving after the initial mammogram is performed and for evaluation of palpable findings. Ultrasound is also used as the imaging modality for initial evaluation of palpable abnormalities in women <30 years of age and in women who are pregnant or breastfeeding. MRI of the breast is integral in screening the high-risk patient. Compared with mammography, MRI has increased sensitivity for detecting cancers, although breast imaging requires intravenous gadolinium which is renally excreted and therefore contraindicated in pregnancy. Breast MRI screening is a valid method used for the evaluation of dense breast tissue and in familial breast cancer screening and for the presence of multiple tumors to delineate disease extent [22].

1.3 The need for this study

Effective use of health-care resources requires knowing which interventions work and how much they cost, and experience with intervention implementation and delivery. One of the first CEA guides for clinicians was written by Detsky and Naglie [26]. CEA compares a new intervention’s costs and outcomes with a current treatment, strategy, or intervention. The main objectives of CEA are to determine the cost of the new intervention compared with current practice and whether the new intervention is more effective. If it is more effective, then the additional benefit is also examined. CEA results
are presented as additional cost per additional benefit (i.e., additional dollars per unit benefit gained) [27].

This study provides additional data on the effectiveness of risk reduction and early detection alternatives in terms of reduction of breast cancer mortality. We evaluated the effectiveness of subcutaneous and total mastectomy as risk reduction mastectomy (RRM) techniques. This study identifies relatively inexpensive interventions that may result in substantial reductions in breast cancer risk and how to redirect resources to achieve these reductions. It demonstrates the benefits of changing resource allocation from ineffective to effective interventions and from less to more cost-effective interventions.

1.4 Objectives and research framework

The objective of this study was to perform an economic evaluation of potential applications of BPM with and without immediate reconstruction in women with a high-risk of breast cancer. The aim was to determine whether these strategies represent value for money for the Canadian health-care system. The research consisted of the following steps:

i). Develop decision-analytic models. These models included decision trees with Markov models as the terminal nodes in the trees. The Markov models were used to simulate monthly transitions among different and distinct health states.

ii). Fit model parameters using three main sources of information (i.e., the Ontario Cancer Registry, Ontario health administrative databases, and secondary sources such as the existing literature) to estimate additional model parameters (e.g., QOL) for various health states.

iii). Set up the models to perform CEAs of different management strategies in women who are at high-risk of breast cancer. The results were presented as incremental cost-
effectiveness ratios, which indicate the average cost per additional unit of health benefit. The health effects outcomes were measured as QALYs. The life years were weighted by utility estimates to obtain the QALY values. The cost outcomes were measured as the mean cost per patient.

iv). Conduct one, two, and three-way deterministic sensitivity analyses of parameters of interest to characterize uncertainty in the output measures and determine the minimum conditions in terms of cost and accuracy for which a management strategy would be cost-effective.

v). Use Monte Carlo simulations (1000 iterations) to conduct probabilistic sensitivity analysis to understand the robustness of the results. For each model input, each iteration consisted of a random draw from an appropriate distribution to produce a distribution of model outputs.

vi). Conduct value-of-information analysis [28,29] as part of the sensitivity analysis to determine the expected monetary value of perfect information about different management strategies in Canadian women at high-risk of breast cancer. Probabilistic baseline decision models were set up to express different strategy-related parameters (i.e., sensitivity and specificity) as probability distributions (i.e., reflecting uncertainty in the Canadian setting) based on available validation analyses. Simulation techniques (i.e., making random draws from the probabilistic model) were used to assess the levels of model uncertainty. A willingness-to-pay threshold [30] was included in the evaluation to determine the opportunity costs associated with BPM with and without different reconstruction techniques. This study provides policy makers who make health care-related resource allocation decisions with important relative cost information. This information will help them determine the combination of interventions that will result in the greatest improvements in health care in Canada.
Chapter 2
Review of Literature

2.1 Epidemiology of breast cancer

Breast cancer is the most leading cause of mortality in women and the second most common cause of cancer-specific mortality in women. Results of reviews of 2008 data from population-based cancer registries indicate that there were approximately 1,384,155 new cases worldwide and almost 459,000 breast cancer-related deaths [31]. The rates of breast cancer diagnoses and of the mortality associated with the disease are increasing worldwide [32]. This result indicates that since 2008 there was a nearly 18% increase in incidence and mortality [1]. During their lifetime, an estimated one out of eight women in Canada will develop breast cancer; translating into approximately 26,300 women and 320 men in Canada annually who will receive a breast cancer diagnosis [2,31]. Canadian Cancer Statistics 2017 estimates that from these, 5,000 women and 60 men will die from their disease [2]. It is estimated that by 2050, the worldwide annual incidence of new diagnoses of female breast cancer will be 3.2 million cases [33]. There is therefore an urgent need for measures to prevent and treat breast cancer.

2.1.1 Tumor features

Breast cancer is a genetically and clinically heterogeneous disease [34]. Tumor size has long been recognized as an important indicator of prognosis. Larger tumors are associated with poorer rates of survival, compared with tumors that are smaller [35,36]; The absence or presence of metastases to the regional lymph nodes also has prognostic importance for disease-free and overall survival times. Regional metastasis is partially a function of time [invasive breast cancers are more likely to become node-positive the
longer they exist in the early untreated phase], but nodal involvement may also indicate the presence of a more biologically aggressive breast cancer phenotype [37,38]. The results of one study indicated that increase negative lymph node count predict favorable overall survival (OS) and disease-free survival (DFS) in breast cancer with different lymph node-positive [39]. There is a similar trend for disease recurrence; only 20–30% of node-negative patients experienced recurrence within 10 years, but recurrence occurred for approximately 70% of patients with node-positive breast cancers [36]. Rates of survival decrease as the number of affected lymph nodes increases. Patients with four or more positive nodes have poorer rates of 5-year survival [37,35] and 10-year survival [40], compared with patients with three or fewer positive nodes. Revising the staging system and changes in treatment protocols for systemic disease have resulted in improvements in the survival of patients with lymph node-positive breast cancer [35].

Cancer staging is used to determine the anatomic extent of a cancer based on its natural history. This information is used for therapeutic decision-making and for determining overall prognosis [41]. Tumor-node-metastasis [TNM] staging is determined using the combined score of the three components tumor size [T], regional lymph node involvement [N], and presence of distant metastasis [M] [41]. The clinical TNM classification system is based on evidence acquired from non-invasive diagnostic methods such as physical examination or imaging, or more invasive methods such as biopsy [42]. The clinical classification system is prone to unreliability. There is clinical-pathological agreement on tumor size in only 54% of cases [43], and clinical assessment of lymph nodes is not always accurate [i.e., positive nodes may be impalpable or negative nodes may be enlarged due to benign changes] [44]. Therefore, use of the pathological TNM staging system is recommended. This system incorporates pathologic measurement of tumor size and lymph node status after surgery to remove the primary tumor and lymph nodes [44]. The presence of metastatic disease is not typically assessed histologically, and thus the clinical classification of distant metastasis is usually given by the “M” component [44].

Breast cancers diagnosed at a more advanced stage are associated with a poorer prognosis. One population-based study of all breast cancer cases in British Columbia,
which was performed in 2002, found that 10-year breast cancer survival rates were above 99% for stage 0, 95% for stage I, 81% for stage II, 55% for stage III, and 4% for stage IV cancers [45].

Histologic grade is also strongly associated with breast cancer survival and recurrence, though has historically not been included in formal staging criteria since its relative contribution to overall prognosis above size and nodal status was not clear [46]. The Scarff-Bloom-Richardson grading system Elston-Ellis modification [Nottingham grading system] is the most commonly-used histologic grading system. Its use is recommended by the United Kingdom, the European Breast Screening Pathology Groups, the United States Directors of Anatomic and Surgical Pathology, the World Health Organization, and the Union for International Cancer Control [44]. Histologic grading accounts for three morphological features [i.e., tubule formation, mitotic count, and nuclear pleomorphism]; each is assigned a score from 1 to 3 [47]. A tumor is considered well-differentiated if the overall score is 3 to 5 [histologic grade I], moderately-differentiated if the score is 6 to 7 [histologic grade II], and poorly differentiated if the score is 8 to 9 [histologic grade III]. Rakha and colleagues examined the association between histologic grade and overall survival time. Survival time was significantly decreased for cancers with a histologic grade of II versus I and III versus I. Rates of disease-free survival were also poorer for breast cancers with a higher histological grade, though this association was only statistically significant for grade III versus I [46]. A high mitotic activity index (reflected in the mitotis count portion of the histologic grade) is also independently associated with a poorer prognosis [48].

Lymphovascular invasion refers to the presence of tumor emboli within blood vessels or lymphatic vessels. While not currently included in most staging systems, prognostic indices, or treatment guidelines, some studies have found that lymphovascular invasion decrease survival time [49-52]. Similarly to lymph node involvement, lymphovascular invasion may have the same predictive power for survival [44].

2.1.2 Histological type
Breast cancer is a heterogeneous disease. It has marked variability in clinical presentation and behavior. Histologic typing may confer biological and prognostically meaningful information [53], in addition to that inferred using tumor morphology alone. Invasive ductal carcinoma of no special type [NST] accounts for 40% to 75% of invasive breast cancers; it is the most commonly diagnosed carcinoma of the breast [54]. An NST diagnosis is made based on exclusion of other adenocarcinomas that do not exhibit the characteristics required to warrant classification as a special type. Special types account for approximately 25% of all breast cancers, and 18 special types are currently recognized by the World Health Organization [54]. Some special types, including tubular, mucinous, invasive cribriform, medullary, infiltrating lobular, and tubulo-lobular breast cancers, have more favorable prognoses compared with NST [55,56]. These cancers are typically diagnosed at the grade 1 stage and have 10-year survival rates that generally exceed 80% [56]. Other special types, such as mixed or solid lobular, mixed ductal and lobular, and ductal/NST have substantially lower rates of 10-year survival [56]. The 10-year population survival rate for patients with inflammatory breast cancer is approximately 30% [57].

2.1.3 Molecular factors

Breast cancers are further classified by their expression levels of estrogen receptor [ER] and progesterone receptor [PR] steroid hormone receptors. ER and PR levels are assessed using immunohistochemistry, while expression of human epidermal growth factor receptor 2/neu [HER-2] is assessed using both immunohistochemistry and fluorescence in situ hybridization [58-59]. ER is expressed in 60–80% of invasive breast tumors and over one-half of ER+ tumors are also PR+ [55,60]. Less than 10% of tumors are ER-/PR+ [60]. The v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 [ERBB2] oncogene, or the human epidermal growth factor receptor 2 [HER-2/neu] oncogene, is amplified in approximately 20% of invasive breast tumors, leading to HER-2 overexpression [55]. Compared with patients who have ER+/PR+/HER-2- tumors, patients with ER-/PR-/HER-2+ [Her2 positive] and ER-/PR-/HER-2 [triple negative]
tumors are significantly more likely to have a late-stage diagnosis and a higher histologic grade tumor, after adjusting for age [61].

Triple negative tumors also have low rates of overall and disease-free survival [61-63]. ER, PR, and HER-2 receptor expression status are used to indicate which molecular pathway affects a tumor and to determine the choice of endocrine therapy. ER+/PR+ [early-stage and metastatic] cancers are treated using anti-estrogenic endocrine therapies such as adjuvant tamoxifen (selective estrogen receptor modulator) or an aromatase inhibitor [28,64]. These treatments have response rates of 60% to 70%. ER-/PR- tumors have hormone therapy response rates of less than 10% [55]. ER+/PR- tumors have intermediate response rates of approximately 40%. Tumors with receptor overexpression or gene amplification of HER2 are treated using anti-HER2 therapies, such as trastuzumab, which improve chemotherapy response in patients with HER2+ breast cancers [65]. No specific drug therapy has been identified for treatment of triple negative tumors, and thus chemotherapy remains the mainstay for treatment of these cancers [65].

2.1.4 Familial breast cancer

Except for age, a family history of the disease is likely the most important risk factor for breast cancer development [66]. Compared with women who have no relatives affected by breast cancer, women who have one affected first-degree relative are approximately two times more likely to develop the disease [67]. The risk increases if more than one first-degree relative is affected or if the relative has a diagnosis at a younger age [4,66,67]. Women with an affected mother and one affected sister have approximately three times the risk compared with women with no family history. Women with three or more affected first-degree female relatives have nearly four times the risk [4,66]. While rare, a first-degree family history of breast cancer in a male family member may further increase the risk [67]. The risk associated with second-degree female relatives having the disease is lower [relative risk [RR] = 1.5, 95% confidence interval [CI]: 1.4–1.6]
compared with the risk conferred by having a first-degree family history [66]. A woman who has a first-degree relative with ovarian cancer has approximately twice the chance of developing breast cancer, compared with a woman who has no affected relatives [68].

Results of studies performed in the United States indicate that approximately 7% to 11% of the general population of women have a first-degree family history of a breast cancer diagnosis [69-71]. Extrapolated to the female populations of Canada and Ontario 20–79 years of age in 2017; 911,102 to 1,382,731 Canadian women and 353,704 to 555,820 Ontarian women had a first-degree family history [2].

Many studies that have examined differences in the prognostic features of breast cancers between women with and without a first- or second-degree family history have found no statistically significant differences [72-77]. However, a few studies have found that compared to women without a family history, women with a familial risk have smaller tumors that are more often node negative and ER+ [78-81]. These results may explain why some studies have found a survival benefit in women with a family history of the disease [79-81].

Women with a family history with breast cancer have a greater risk of high-risk forms of benign breast disease [BBD] such as atypical hyperplasia [82]. This increase in risk is greater in younger women [82-84]. Having a family history of breast cancer and a diagnosis of a severe type of BBD [i.e., proliferative lesions without atypia or atypical hyperplasia] increases the risk of developing breast cancer, compared with having no family history, but having a similar BBD diagnosis [85,86].

2.1.5 Epidemiology of breast cancer in Canada

In Canada, breast cancer is the most frequently diagnosed malignancies in women. There were approximately 26,500 new diagnoses in 2017, which represented 25.5% of all the newly diagnosed cancers in women [2]. In Canada, breast cancer incidence has increased
throughout the early 1990s. This increase is likely due to increases in the use of screening mammography [2]. Since 2004, breast cancer incidence has stabilized in Canada [2]. The lifetime probability of having a breast cancer diagnosis for Canadian women of all ages is 12.4% [2]. In 2017, there were 10,100 new breast cancer diagnoses and 1,900 breast cancer deaths in Ontario [2]. The breast cancer prevalence was just below 1.0% in 2010, with approximately 63,000 women in Ontario having a breast cancer diagnosis sometime during the 10 years leading to the beginning of 2010 [2].

Breast cancer ranks second [following lung cancer] in female cancer mortality in Canada [2]. Age-standardized mortality rates for deaths from female breast cancer have been declining since the mid-1980s. There was a projected relative reduction of 55%, from 41.7 per 100,000 women in 1988 to 23.3 deaths per 100,000 women in 2017 [2]. This change likely resulted from increased participation in breast cancer screening [mammography], combined with the use of targeted adjuvant therapies following breast cancer surgery [2]. Similar declines in rates of breast cancer mortality have also been noted in the United States, United Kingdom, and Australia [87].

2.2 High-risk breast cancer

The general average population risk of a breast cancer diagnosis is 1 in 8 to 1 in 12 [88], and age, family history, endocrine exposure, breast density, radiation to chest wall and a history of one or more benign proliferative breast disorders can considerably increase the risk. Mutations in moderately or highly penetrant cancer susceptibility genes that result in an inherited predisposition are responsible for approximately 5% of breast cancer cases [89]. Discovery of specific germline genetic susceptibility factors [e.g., mutations in the BRCA family of tumor suppressor genes] is important for accurate risk assessment results. The lifetime risk of developing breast cancer in women who carry these genes is 40%–87%, and the cancer typically occurs at a younger age [90-92]. The definition of ‘high risk’ is inconsistent in the medical literature. This variability presents an important
challenge to successful evidence-based management of high-risk women. A ≥25% lifetime risk has traditionally been used as the definition of ‘high risk’ in the Canadian context [93], although some studies define high-risk as a ≥20% lifetime risk [94]. Prevention research, cancer screening, and/or clinical practice have tended to stratify risk into an inherited type [i.e., genetic or ‘familial’ risk] of risk category and a personal risk factor-based risk category [95].

2.2.1 Breast cancer risk assessment models

Since 1995, breast cancer risk assessments have increasingly become included in routine medical care. Individuals at elevated risk of breast cancer are identified and offered a different approach for prevention and screening. Statistical models to assess individual risk and to accurately estimate population risk have been designed and validated [96-151].

There are two main approaches in breast cancer risk models that can be used to assess risk. Current risk prediction models quantify a woman’s risk based on risk factor combinations and is estimated over a time interval [i.e., a 5-year interval, a 10-year interval, or lifetime risk] [96-133]. Models that provide a probability that a woman has a mutation in a gene known to cause a hereditary cancer predisposition syndrome are also used for risk estimation [134-151].

These model types can be further subdivided into the two broad categories of empirical and genetic models [20,152]. Empirical breast cancer risk models combine personal or family history factors, or both, to estimate the probability of detecting a BRCA1 or BRCA2 mutation. They do not include genetic factors such as mode of inheritance, mutation prevalence, or penetrance [i.e., the chance of developing cancer in someone carrying a gene mutation]. The Gail model is the most well-known and often-used breast cancer risk assessment model [103]. Other empirical models include the Shattuck-Eidens
model [the Myriad I model] [151] and the Couch model [Penn Model]. The Couch model [updated as the Penn II model] now includes more family and personal variables relating to cancer history [153]. The details about the development and validation of the Penn II model remain unpublished. The Myriad II model [the Frank model] is one of the empirical models derived from the Myriad Genetic testing program [139,140]. The Myriad II is based on genetic testing of >10,000 individuals [139]. Two similar models were developed to simplify the use of these models [i.e., the Manchester model [143] and the family history assessment tool [154]. Another group of empirical models includes the LAMBDA model [144] and the National Cancer Institute model [196]. These models were developed for use in Jewish women of Eastern European descent [Ashkenazi Jews]. The models developed from data collected in Spain [146] and Finland [148] are also used for risk assessment. Results of an analysis using a Spanish dataset indicated that these scoring system models and the Myriad II model have similar discriminatory power. Compared with models that are not aimed at specific populations, models intended for use for specific populations do not have better discriminatory accuracy [155].

Genetic risk prediction models, as discussed by Amir and colleagues [20], include assumptions about susceptibility gene numbers, cancer risks caused by gene mutations, and mutation frequencies in the general population. The primary advantage of these models is that they can be used to estimate mutation carrier probabilities and cancer risks without requiring information about the family structure and disease pattern [20]. Genetic models provide a probability that a woman has a mutation in a gene known to cause a hereditary cancer predisposition syndrome. Hereditary breast and ovarian cancer syndrome [i.e., the BRCA1 and BRCA2 genes] and Cowden syndrome [PTEN gene] models include assumptions about the numbers of cancer susceptibility genes, the population-wide allele frequencies, and the risks associated with the alleles. Specific within-family relationships are included in the pedigree analysis methods that are used in the models. The underlying assumptions of the models affect the accuracy of the risk prediction. Approximate risk estimates are produced by the current models used because additional genes that affect breast cancer susceptibility remain to be identified [152]. The BRCAPRO model is the most used and validated of the group [136,156,157]. The International Breast Cancer Intervention Study [IBIS] model [Tyrer–Cuzick model]
The Yale University model [158], and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA] [135] are other validated and commonly used models.

BRCA1 and BRCA2 risk estimation models [136,156-162] have been validated and compared. The empirical and genetic models have high discriminatory power between mutation carriers and non-carriers, but the between-model and between-population sensitivity and specificity varies [163]. In one study, the five models most frequently used for populations in the United Kingdom [i.e., BOADICEA, BRCAPRO, IBIS, Myriad II, and Manchester] were used to compare data from six genetics clinics in the United Kingdom [134]. The BOADICEA was the only model that accurately predicted the overall observed number of mutations that were detected in the patient populations. It also had the best between-group [i.e., mutation carriers versus non-carriers] discriminatory power. The difference was statistically significant between the BOADICEA and all the other models, except the BRCAPRO [area under the curve [AUC]: BOADICEA = 0.77, BRCAPRO = 0.76, IBIS = 0.74, Manchester = 0.75, and Myriad II = 0.72]. The numbers of BRCA1 and BRCA2 mutations in populations with a low estimated risk of having BRCA1 or BRCA2 mutation carriers were underestimated by all models, including the BOADICEA model. The BRCAPRO, Penn II, Myriad II, Couch, family history assessment tool, BOADICEA, Manchester, and IBIS models were compared using a single-institution study, which was performed in Toronto, Canada. The results indicated that all except the Manchester, IBIS, and Couch models had similar and good discriminatory accuracy [AUCs all approximately 0.75]. The AUC values for discriminatory accuracy for the Manchester and IBIS models were 0.68 and 0.47, respectively. Compared with the other models, the Penn II model had higher diagnostic sensitivity at the 10% testing threshold for assessment of the probability of carrying a mutation [164].

The limitations of risk assessment models that reduce their accuracy and validity include small family size, adoption, and lack of family history information [165]. The genetic risk assessment models generally underestimate cancer risk because they include data about first- or second-degree relatives, but not about more distant relatives. Prostate and
pancreatic cancer are examples of two types of cancer that are not included in the family history assessments of some models. These cancers are also affected by BRCA1 or BRCA2 mutations [165].

Amir and colleagues used a prospective analysis to compare the Gail, BRCAPRO, and IBIS cancer risk models. Fifty-two cancers were recorded in a population of 1,933 women who attended a family history clinic [166]. They calibrated the BRCAPRO model to use the Claus [89] and Ford [91] mutation prevalence estimates. The investigators used data collected during a mean follow-up of 5.27 years to derive the model inputs and obtained estimates of breast cancer risk. The results [i.e., ratios] for the expected to observed numbers of breast cancers were 0.48 [95% CI: 0.37–0.64] for the Gail model, 0.56 [95% CI: 0.43–0.75] for the BRCAPRO [Claus] model, 0.49 [95% CI: 0.37–0.65] for the BRCAPRO [Ford] model, and 0.81 [95% CI: 0.62–1.08] for the IBIS model. Receiver operating characteristic curves were used to evaluate the accuracy of the models for individual assessment [AUC = 0.735, Gail; AUC = 0.716, BRCAPRO [Claus]; 0.737, BRCAPRO [Ford]; 0.762, IBIS]. The IBIS model was the most consistently accurate for breast cancer risk prediction [166]. The results of subgroup analyses indicated that the Gail, BRCAPRO [Claus], and BRCAPRO [Ford] models underestimated breast cancer risk, especially during individual assessment of women with one first-degree relative with breast cancer. In this subgroup of women, risk prediction was accurate when the IBIS model was used. All models were accurate for risk prediction for women who had two first-degree relatives or one first-degree relative and two other relatives with the disease [166]. Taken together, these results suggest that having one affected first-degree relative affects risk more than predicted.

The only models that accurately predict breast cancer risk in women with a family history of ovarian cancer are the BRCAPRO [Ford] and IBIS models [167]. Analyses using these models include a woman's family history of ovarian cancer. Therefore, a family history of ovarian cancer has a substantial effect on risk. The values for risk in women who were nulliparous or whose first live birth occurred at >30 years of age were underestimated by the Gail, BRCAPRO [Claus], and BRCAPRO [Ford] models; the results were statistically significant [166,167]. The Gail, Claus, Claus extended, Jonker, IBIS, and BOADICEA
models were included in a more recently published retrospective analysis. The Gail, Claus, and Jonker models underestimated breast cancer risk. Taken together, these results suggest that the IBIS and BOADICEA models are the most accurate models available for assessment of breast cancer risk, these are the models used in Ontario by CCO [165-167].

2.2.2 Genetic counseling

A complex interaction of genetic, genomic, and environmental factors results in the initiation and progression of breast cancer [168]. Since 1995, specific genes have been recognized as associated with hereditable breast and gynecologic cancers, and the need for cancer genetic counseling has consequently grown [169]. Individuals who have cancer predisposition gene mutations and family and personal histories that affect overall risk are identified by genetic counselors. Counseling is an important part of the risk assessment process and accurate information and emotional support can be provided to individuals who have inherited deleterious mutations present in parents or siblings as well as to those who may have a generalized increased risk for cancer development with and without having inherited any specific mutations [169]. Counselors use different risk assessment approaches to evaluate individual risk for carrying a deleterious cancer susceptibility gene. Counselors provide nondirective counseling concerning the decision to undergo genetic testing or to initiate screening, diagnostic, or preventative measures. They also perform psychosocial assessments because patients often endure psychological upset and emotional stress when the results of the counseling and testing are revealed. Before counseling and risk assessment proceeds, counselors should obtain information from patients regarding expectations about the counseling experience, perceptions about the effects of the cancer[s], the economic effects of counseling and testing and the possible clinical outcomes, as well as their relationships with relatives and their ability to get information from those relatives. In the case where an increased risk for cancer is
determined, the counselor should also determine if the patient has the desire to implement lifestyle changes and preventative measures.

US Preventative Services Task Force [21] guidelines for when to refer a patient for genetic counseling and testing include having two first-degree relatives with breast cancer, at least one diagnosed at ≤50 years of age; three or more first- or second-degree relatives with a breast cancer diagnosis; any pattern of breast and ovarian cancer among first- and second-degree relatives; a diagnosis of bilateral breast cancer in a first-degree relative; a diagnosis of ovarian cancer at any age in two or more first- or second-degree relatives; both a breast and ovarian cancer diagnosis, regardless of age, in a first- or second-degree relative; a breast cancer diagnosis in any male relative; a woman of Ashkenazi Jewish heritage who has a first-degree relative [or any two second-degree relatives] who had a diagnosis of breast or ovarian cancer [21].

2.2.3 Familial breast cancer risk

The first of many reports of a familial pattern of breast cancer was published in 1866 [170]. One family member had early-onset carcinoma of the breast, and a pedigree analysis revealed that four generations of family members also had the disease. Breast cancers arising from a hereditary cancer susceptibility syndrome [i.e., caused by mutations in high-penetrance susceptibility genes] are seen in only approximately 5% of all breast cancer cases. Approximately 16% of presumed hereditary breast cancers are due to germline mutations in the BRCA1 or BRCA2 early-onset genes [172,173]. The BRCA1 and BRCA2 genes were identified in 1994, and since then a few other high-penetrance breast cancer susceptibility genes have been described [174].

A meta-analysis performed by Antoniou et al. revealed that BRCA1 mutation carriers have a 65% [95% CI: 44%–78%] lifetime breast cancer risk and a 39% [95% CI: 18%–54%] lifetime ovarian cancer risk. BRCA2 mutation carriers have a 45% [95% CI: 31%–
56%] lifetime breast cancer risk and an 11% [95% CI: 2%–19%] lifetime ovarian cancer risk [90]. Associations between BRCA2 mutations and an increased risk of pancreatic, gastric, bone, prostate, laryngeal cancers, and melanoma are significantly elevated [139,175-178]. Numerous studies have investigated mutation penetrance, and some lifetime risk estimates for carriers of either BRCA mutation exceed 80% [138,179,180]. Penetrance estimates differ by method of case ascertainment; family studies tend to produce higher estimates than studies based on cases unselected for family history [181]. The penetrance of BRCA1/2 mutations is high, but these mutations are rare. In the general population, the estimated carrier rate is 1 in 345 to 1 in 1000 [173,182,183]. The values for BRCA1/2 mutation prevalence are higher among specific geographic and ethnic sub-populations [184,185]. Clusters of BRCA mutations have also been identified in the Netherlands [186], Iceland [187,188], Sweden [189], and the Bahamas [190].

Mutation carrier status is also linked to breast cancer outcomes. Numerous studies have investigated prognosis in BRCA-associated breast cancers. The results of some early studies suggested that patients with BRCA-associated breast cancer have a better prognosis, compared with patients with a sporadically-occurring cancer type [191-194]. Later studies using more rigorous methodologies [i.e., larger sample sizes, inclusion of important prognostic factors, adjustment for treatment type] found that BRCA-associated cancers have a poorer prognosis [195-199]. A review of this evidence suggests that the overall prognosis for patients with BRCA-associated breast cancer is similar to the prognosis for patients with sporadic breast cancer [200]. However, contralateral breast cancer risk is higher in patients with BRCA-associated breast cancers [201,197]. Survival may depend on whether adjuvant chemotherapy is administered [195,196].

2.2.3.1 BRCA1 and BRCA2 gene and multi-gene panels
In 1990, linkage analysis revealed that the BRCA1 gene [chromosome 17q21] was associated with breast cancer in a large group of families with members affected by early-onset disease [202]. The gene was cloned in 1994, and researchers found that in families with more than one case of breast cancer, the BRCA1 coding sequence contained truncating mutations [203]. The BRCA2 gene [chromosome 13q12.3] was found in 1995. Linking analysis and positional cloning were used to examine breast cancer pedigrees in successive generations of families [204,205]. The BRCA2 mutation was also found in families with high frequencies of male members with breast cancer [202-205].

In addition to increased breast and ovarian cancer risks, the risks of fallopian tube, gastric, colon, melanoma, prostate, and pancreatic cancer are increased in individuals with BRCA1 and BRCA2 mutations [206-212].

BRCA1 and BRCA2 are separate and distinct tumor suppressor genes that cause approximately 5% of all cases of breast cancer [213] and 85% of all hereditary breast and epithelial serous ovarian cancer cases [214]. In the absence of epithelial serous ovarian cancer in the family pedigree, BRCA1 and BRCA2 are responsible for a smaller percentage of familial breast cancer cases [215,216]. The general population frequencies of mutations in these two genes is approximately 1/300 to 1/800 [183]. However, results of a study by Risch and colleagues in Canada suggested that these frequencies may be considerably higher, at 1/140 to 1/300 [92]. Some populations and communities have higher frequencies of specific BRCA1/2 mutations compared with the general population [183,92].

Family linkage studies have identified additional high-penetrance genetic mutations on the phosphatase and tensin homolog [PTEN] and tumor protein 53 [TP53] tumor suppressor genes [217]. Female carriers of the TP53 mutation have a breast cancer risk of approximately 30% by 30 years of age [218], and 50% by 50 years of age [219].

Mutations on ataxia telangiectasia mutated [ATM] kinase, checkpoint kinase 2 [CHEK2], RAD51 paralog C [RAD51C], BRCA1 interacting protein C-terminal helicase 1 [BRIP1], and partner and localizer of BRCA2 [PALB2] are associated with a moderate increase [20% to 40%] in the lifetime risk [217,218]. Commonly-occurring low-penetrance alleles
associated with slightly increased or decreased risk have been identified by genome-wide association studies [GWAS] [217,218]. Only 5% to 10% of breast cancer cases likely result directly result from genetic mutations; BRCA1 and BRCA2 mutations account for the largest proportions [2% to 5% of all breast cancers on a population level] [219].

Approximately 5%–10% of the patients who undergo testing for BRCA1/2 mutations have a variant of uncertain clinical significance [VUS] [220]. More than 1,500 VUSs have been identified and are frequently identified in individuals in minority ethnic populations. Most VUSs have only been reported in one to two individuals, so analysis of the clinical effects of VUSs is challenging [221]. Once a VUS is identified, further analyses such as segregation analysis or analysis of study variants in multiple unrelated individuals are used to characterize the VUS as clinically relevant [favor deleterious] or irrelevant [favor polymorphism] [220,221]. However, small family sizes and few individuals with any particular VUS impede the mathematical estimation needed to better characterize the clinical effects of a specific VUS [221]. A VUS finding is difficult to manage clinically because it can lead to considerable emotional distress concerning the unknown clinical implications of the genetic test result. Counselors must use their skills to provide a clear and measured overview of the meaning and implications of the test and provide emotional support for a patient who may be distraught because a definitive assessment of risk cannot be given [221,222].

2.2.3.2 Tumor characteristics in familial breast cancer

2.2.3.2.1 Tumor characteristics of BRCA1-related breast cancer

The histopathological characteristics of BRCA1-associated breast cancers differ from the characteristics of sporadic breast cancers. Invasive ductal adenocarcinoma is the most common [74%] BRCA1-associated tumor, while 2% of sporadic breast cancers versus
13% of BRCA1-associated tumors are medullary-like carcinomas [223]. The frequencies of other histological types are similar between BRCA1 and sporadic tumors. Compared with the sporadic tumors, BRCA1 tumors tend to have higher mitotic counts, be more poorly differentiated [grade 3] and have higher numbers of necrotic areas in a given tissue sample [224]. The BRCA1 tumors have characteristics of more aggressive phenotypes; they have less tubule formation but have more pleomorphism [192,223-226]. They have high rates of lymphovascular invasion, tend to be well-demarcated, and have high degrees of lymphoplasmacytic infiltration [227].

Statistically significant differences in grade [higher] and in percentage of medullary type tumors [more cases] are present in the younger population [<50 years of age] compared with the older population [≥50 years of age] of BRCA1 mutation carriers who develop breast cancer [228]. Initially, it was reported that compared with non-carriers, the BRCA1 mutation carriers have lower rates of ductal carcinoma in situ [DCIS] [41% for non-carriers and 2% for carriers] and lobular carcinoma in situ [LCIS] [56% for non-carriers and 6% for carriers]. However, these estimates were developed from cases of invasive breast cancer that contained non-invasive disease within it [229]. Results of analyses of tissue from prophylactic mastectomy (PM) of BRCA1 mutation carriers indicated that non-invasive disease occur more frequently in carriers [e.g., DCIS [230-232], LCIS [230], atypical ductal hyperplasia [ADH] [230-232] and atypical lobular hyperplasia [ALH] [230-232] , usual ductal hyperplasia , columnar cell lesions [232], and fibroadenoma [233,234]. Breast cancers of BRCA1 mutation carriers are likely to have ER [ER] overexpression and low progesterone receptor [PR] expression [228,235,236].

human epidermal growth receptor 2 [HER-2/neu] , epidermal growth factor receptor [EGFR], Cyclin D1 [CCND1] ,are major oncogene in breast cancer , Compared with control cancers, human HER-2/neu expression is usually low in BRCA1-related breast cancers, and there are few reports of amplification of HER-2/neu [226,235]. Because HER-2/neu is near BRCA1 on chromosome 17, HER-2/neu may be lost during loss of heterozygosity at the BRCA1 locus [237-239]. Compared with HER-2/neu, EGFR overexpression is strongly associated with BRCA1-associated breast cancers [240,340].
Cyclin D1 [CCND1] is often not expressed in the BRCA1-related breast cancers [242]. tumor protein TP53 gene mutations which plays an important role in cell cycle control and apoptosis, are detected in 30%–77% and approximately 20% of BRCA1 tumors and sporadic controls, respectively; TP53 often accumulates in BRCA1 tumors. The BRCA1 and BRCA2 genes might affect the distribution of TP53 mutations [235,243].

BAX and BCL2 are apoptosis-associated proteins that have lower expression in BRCA1 breast tumors compared with sporadic malignant breast tumors [246,247,239], but BRCA1 tumors have high levels of caspase 3 activity [247]. The hypoxia response is mostly controlled by the key regulator hypoxia inducible factor-1α [HIF-1α], which is correlated with a poor prognosis and is overexpressed during sporadic breast carcinogenesis [248-250]. HIF-1α is overexpressed in most BRCA1-related breast tumors [251]. The BRCA1-associated breast tumors likely have an increased cancer stem cell population compared with sporadic cancers, stem cell marker ALDH1 expression is higher in the BRCA1 tumors [252]. M.R. Heerma van Voss compared breast tumors with normal breast tissue among healthy control breast specimen and found that there are no differences in HIF-1α expression in normal breast tissue of BRCA1 mutation carriers [252]. Taken together, the results of studies of this immunophenotype indicate that the BRCA1-associated tumors have the breast progenitor cells’ immunophenotype, so the BRCA1s might be derived from these cells [227,253]. The immunophenotypes of the pre-invasive lesions in the BRCA1 carcinogenetic spectrum remain to be determined [227]. The immunophenotype of accompanying invasive cancers is similar to the BRCA1 carrier DCIS immunophenotype [253].

Higher rates of brain and lung metastases and lower rates of bone metastases have been found in patients affected by BRCA1 tumors [199]. The results of studies comparing BRCA1 breast cancer with age-matched sporadic breast cancer patients indicate that survival rates are lower for BRCA1 patients in some populations but are similar in other populations [194,197].

Breast cancer subtypes can be differentiated using gene expression profile analysis [254,255]. These analyses have revealed that BRCA1-related breast cancers are typically
the basal subtype; they express basal markers [e.g., CK 5/6, CK14, EGFR, P-cadherin, caveolin 1, vimentin, and laminin] [240,244]. These results indicate that in BRCA1 germline mutation carriers, carcinogenesis frequently occurs along the “basal” progression route. BRCA1 germline mutation-associated breast tumors have less promotor hypermethylation of tumor suppressor genes than do sporadic tumors, but the rate is still higher when compared with the rate in normal tissue [256].

Compared with the tumors used as sporadic controls, the BRCA1 tumors have a different pattern of chromosomal copy-number gains and losses [e.g., gains of 3q, 7p, 8q, 10p, 12p, 16p, and 17q and losses of 2q, 3p, 4p, 4q, 5q, 12q, 16p, and 18q]. This pattern has only a partial overlap with the copy-number changes in the sporadic and BRCA2 germline mutation breast tumors [257-258].

2.2.3.2.2 Tumor characteristics of BRCA2-related breast cancer

Like BRCA1-associated tumors, invasive ductal carcinoma is the most common histological type found in BRCA2 tumors [76%]. Compared with sporadic breast cancers, invasive [pleiomorphic] lobular, tubular, and cribriform carcinomas have been reported at higher incidence rates for BRCA2-associated breast cancers [192,223,225,962]. Compared with controls, they have more nuclear pleomorphism, less tubule formation, and higher mitotic rates, which results in a carcinoma that is poorly- or moderately-differentiated [grades 2 and 3] [223,239]. Also similar to the BRCA1s, the BRCA2 breast tumors have a greater proportion of continuous pushing margins [i.e., compared with the sporadic breast cancers] [223,259]. In BRCA2 mutation carriers, the pre-invasive DCIS and LCIS tumors occur at the same frequencies [52% and 3%, respectively] compared to sporadic patients’ tumors [56% and 6%, respectively] [229,260,261]. Compared with BRCA1 mutation carriers, tissue from PMs of BRCA2 carriers can range from no difference to more frequently occurring premalignant lesions [e.g., DCIS, LCIS, ALH, ADH, and columnar cell]. The same lymph cytoplasmic infiltration found in invasive
BRCA2- and BRCA1-related cancers has also been found in DCIS lesions, and T-cell lobulitis is also present in normal breast tissue [230,234].

Sporadic and BRCA2 breast cancers have similar immunophenotypes, so most BRCA2 tumors have an immunophenotype different from the BRCA1-associated breast tumors. ERα and PR are expressed at higher rates in BRCA2 cancers [228,240]. As patient age increases, the probability of having an ER-positive BRCA2 breast cancer decreases [242]. Compared with sporadic breast cancer, there is no or low expression of HER-2/neu in BRCA2 cancers; HER-2/neu amplification is only rarely found [239-241]. Levels of fibroblast growth factor 1 [FGF1] and fibroblast growth factor receptor 2 [FGFR2] expression are higher in the BRCA2 compared with the BRCA1 breast cancers. Physicians might use this difference to differentiate the BRCA2 breast cancers from others. Typically, only “luminal” cytokeratins [e.g., CK8 and CK18, and not CK5/6 and CK14] are expressed in the BRCA2 breast cancers [247]. No caveolin1 expression has been described [239]. Compared with the BRCA1s, p53 incidence is the same or lower for the BRCA2 breast cancers [247]. Compared with BRCA1 and non-BRCA carriers, BAX, cyclin D1, and BCL2 expression can be greater in the BRCA2-related breast cancers [239,247]. BRCA2-related cancers also can have high EGFR expression [based on anecdotal evidence]. No results suggest that BRCA2-related carriers are positive for HIF-1α, P-cadherin, vimentin, or ALDH1 expression [253].

Invasive BRCA2-related cancer immunophenotypes have been well-studied, but immunophenotypes of the pre-invasive BRCA2 carcinogenetic spectrum lesions have not. The DCIS immunophenotypes in BRCA2 carriers and in accompanying invasive cancers are similar [253].

Unlike the BRCA1 breast cancers that likely originate from progenitor cells, most of the BRCA2 related breast cancers are luminal type cancers and overexpress PR, ER, CK8, and CK18. Therefore, it is likely that these cancers originate from breast luminal cells rather than progenitor cells [239-241].

The ER positivity is likely associated with the bone and soft tissue metastases that affect women with BRCA2-related breast cancer [199]. Similar to the studies that attempted to
predict outcomes in BRCA1 patients, the results of studies that examined outcome for BRCA2 patients have been conflicting [194-197].

Discriminating genes [i.e., transcription, signal transduction, cell adhesion and proliferation, and extracellular matrix remodeling] were examined using gene expression analysis to study unique characteristics of BRCA2-associated tumors [261-263]. The relatively high levels of expression of FGF1 and FGFR2 were confirmed using immunohistochemistry. Most of the BRCA2-related breast cancers examined were found to be of luminal origin [254,255]. Chromosomal copy-number gain and loss patterns are present in BRCA2 breast cancers that are not present in sporadic controls [i.e., gains of 8q, 17q22-q24, and 20q13, and loss of 8p, 6q, 11q, and 13q] [257,258].

2.2.3.2.3 Tumor characteristics of non-BRCA1- and non-BRCA2-related breast cancers

The cancers of patients with a strong family history of breast cancer but without BRCA1 or BRCA2 germline mutation have various phenotypic characteristics and result from mutations in low- to moderate-penetrance genes or undiscovered genes. Compared with the sporadic breast cancers, these tumors are typically an lower grade and the immunophenotype is approximately similar to that for sporadic breast disease [264,265]. The results of a study that classified non-BRCA-related breast cancers into two homogenous subsets indicated that ribosomal genes were more frequent in one group compared with the other, based on a 60-gene set [266].

2.2.3.3 Penetrance [low, moderate, and high]
Six uncommon but highly penetrant breast cancer genes [e.g., BRCA1, BRCA2, PTEN [267], [268], TP53 [269], [270], [271], CDH1 [272], and STK11 [273], [274], and four rare but moderately penetrant breast cancer genes [CHEK2] [275], BRIP1 [BACH1] [276], ATM [278], and PALB2 [281] have been identified and confirmed. Most of the <30% of the cases with a personal and/or family history of hereditary breast cancer for whom a causative gene mutation has been identified, have a mutation in one of the six highly penetrant genes. These patients are typically managed following specific published guidelines [282]. Some of the cases result from mutations in the moderately penetrant genes. Genetic testing methods have also been used to identify low-penetrance alleles. The low-penetrance alleles should not be routinely screened because they have a polygenic effect in only a small number of cases. Until the gene identification accuracy and the effectiveness of clinical case management improve, a high index of suspicion for a specific etiology should be present before mutation testing is performed [283].

2.2.3.4 Ashkenazi Jewish population risk

Since the 19th century, race has been thought to predispose its members to increased susceptibility to specific diseases [281, 282]. Researchers study different ethnic and racial groups to find between-group differences in disease susceptibility [283]. For example, Jewish people of Ashkenazi descent are predisposed to the development of autosomal recessive disorders [e.g., Tay-Sachs disease] [284,285]. The prevalence of these disorders is greater among those of Ashkenazi descent compared with other groups. Many distinct mutations occur only in this genetically unique group of people [284,286], which represents >90% of the approximately 6 million people of Ashkenazi descent in the United States and Canada.

Compared with non-Ashkenazi Caucasians who are not of Jewish descent, those who are of Ashkenazi descent have a greater risk of breast cancer [287,288] associated with non-genetic and genetic risk factors. The results of a large sample size case–control study [289] indicated that the RR for breast cancer associated with Jewish ethnicity is 1.10 [95% CI: 0.84–1.44]. These women who also have a first-degree relative with breast
cancer or whose breast cancer was diagnosed at <50 years of age have higher RR values for being BRCA mutation carriers [RR: 1.95, 95% CI:0.88–4.63; RR: 1.55, 95% CI: 0.92–2.63, respectively]. BRCA1 and BRCA2 mutations have been found to be present at higher frequencies among Jewish patients. Compared with the general population, the frequencies of these mutations are approximately five times greater among those of Ashkenazi descent and may be affecting 2.0%–2.5% of Ashkenazi Jewish men and women overall [290-294]. About 2.5% of Ashkenazi Jewish descent carry one of three ancient (founder) mutations in BRCA1 or BRCA2 (185delAG or 5382insC in BRCA1 and 6174delT in BRCA2). Founder mutations of BRCA1 or BRCA2 in Ashkenazi Jewish are responsible for the majority of hereditary breast and ovarian cancer and some Ashkenazi families with histories of an inherited cancer have been shown to segregate other (non-founder) mutations of BRCA1 or BRCA2. The information regarding the incidence of these non-founder mutations is limited and it makes Counselling these families difficult [149, 233, 290-292].

2.2.3.5 Male breast cancer

By 2018, The American Cancer Society estimates that in the United States, approximately 2,550 men will receive a diagnosis of breast cancer. These cases of male breast cancer represent 0.5%–1% of all cases of breast cancer, and it is anticipated that among these, 480 will die as a result of their disease [295]. The results of a meta-analysis indicated that men who have a first-degree relative with breast cancer, BBD, or who have Jewish ancestry, are at significantly increased risk of developing breast cancer [296]. Evans and colleagues found that having a gene mutation in the BRCA2 gene is associated with an 8% lifetime risk of breast cancer development in men. All male breast cancer [MBC] patients should undergo a thorough genetics evaluation [297]. An increased risk for developing MBC is seen among BRCA1 and BRCA2 gene mutation carriers, and guidelines recommend that individuals who have a personal or family history of MBC
should be tested for mutations in these gene [298]. Four to 40% of MBC patients have a BRCA2 gene mutation. Mutation in the BRCA2 gene is the most common mutation found in MBC cohorts, depending on the population examined and whether there is a family history of a breast and ovarian cancer diagnosis [139,150,187,299-303]. Males who are BRCA1 and BRCA2 pathogenic mutation carriers have cumulative lifetime breast cancer risks of 1%–2% and 5%–10%, respectively, and the lifetime risks for pancreatic and prostate cancers are also increased in these individuals [304,305].

Only a limited number of studies have examined the associations between MBC risk and other genes. An association between a specific CHEK2 mutation [1100delC] and increased MBC risk was found in two studies [275,306], but the results of other studies were not concordant with this finding [307-314]. The effects of other CHEK2 pathogenic variants are unknown. Other studies have found that MBC patients can have PTEN, androgen receptor [AR], NF1, and PALB2 germline pathogenic mutations, but the clinical significance of these mutations and the risk estimates associated with them remain to be determined [315-318]. The utility of multi-gene panel testing beyond BRCA1/2 is limited in MBC patients, and the validity of any such results has not been determined. The results of a study that included multi-gene panel testing of a group of MBC cases indicated that 31.8% [n = 7/22] had positive test results; 4 (18.2%) had BRCA1/2 mutations, and 3 (13.6%) had other mutations [i.e., PALB2, CHEK2, and ATM] [302].

Anderson and colleagues found in a study published in 2010, based on an analysis of SEER database between 1973–2005, that 92% of the 5,494 MBC cases and 78% of the 838,805 female breast cancer cases were ER-positive [319]. Similar to women, most MBCs are invasive ductal carcinomas [320,321]. Compared with women, papillary carcinomas are more, and lobular carcinomas are less, common in men [322].

Patterns of HER2 status and tumor grade for MBCs are unclear because retrospective study databases contain missing or conflicting data. Anderson and colleagues in their analysis of SEER database between 1973–2000, found that 39% of the 1,180 tumors from men for whom grade was known, were grade 3. This result is consistent with the
proportion of grade 3 tumors seen in postmenopausal women with breast cancer but is less than that found in premenopausal women [323]. A separate smaller study of 41 MBC cases found in contrast that 73% of patients had grade 3 tumors and 45% had HER2-positive tumors [324]. Other studies have found HER2 overexpression rates of 2%–42% [325-328]. Because of the increased risk of BRCA mutations, genetic counseling should be offered to patients with MBC, especially if an individual has a family history of breast or ovarian cancer [315]. The BRCAPRO has been validated for use in patients with MBC [329]. However, compared with the male proband, BRCA testing may have greater clinical relevance for the female family members. Family members of MBC patients have an increased risk of breast cancer [330], especially if other members of the family have had a diagnosis of prostate or other BRCA-related cancers [331,332].

2.3 Breast cancer screening

Breast cancer screening is used for the purposes of detecting the disease at an early stage. Early detection facilitates treatment and the potential improvement in the prognosis may not exist if the disease is detected at a later stage.

2.3.1 Breast cancer screening in Canada

In Canada, mammography is freely available to screen-eligible women through organized screening programs operated at the province level. It is also available opportunistically [i.e., with referral by a physician] through mammography facilities that operate outside of the provincial screening programs [333]. Canada’s first organized breast cancer screening program began in British Columbia in 1988, followed by programs in Ontario, Saskatchewan, Alberta, and the Yukon Territory in 1990 [333]. There now exist
organized breast cancer screening programs in all Canadian provinces and territories except Nunavut, where only opportunistic screening is available [333]. Organized programs provide all women 50–74 years of age, without a prior diagnosis of breast cancer, with a biennial, bilateral, 2-view [cranio-caudal and medio-lateral oblique] screening mammogram that is paid for through a provincially managed universal health insurance plan [333]. Some programs continue to offer clinical breast examinations [CBE] performed by a trained nurse or technologist. However, most provinces have removed CBE from screening programs because of an absence of scientific evidence for mortality benefit [333]. Canada’s organized breast screening programs also facilitate the navigation of women with abnormal or inconclusive screening results through the diagnostic phase, and typically issue recall notices to participants who have normal or non-malignant screening results so that they are advised as to when their next screening mammogram is due [70]. In some cases, screening programs in some provinces and territories also screen women outside of this age group or at more frequent intervals when the patient has a history of breast cancer in a first degree relative, at the request of the health-care provider or client [333].

In 1990, the Ontario Breast Screening Program [OBSP] was established by the Ontario Ministry of Health under the auspices of Cancer Care Ontario. The OBSP offers mammographic screening through self- or physician-referral to average risk women 50–74 years of age [2,334,236].

As of July 1st 2011, the OBSP expanded to include annual combined breast MRI [or breast ultrasound where MRI is contraindicated] and mammographic screening for women at a high breast cancer risk. Ontario was the first region worldwide to offer screening to high-risk women within the context of an organized screening program [2,335]. This expansion was supported by clinical practice guidelines that suggest that high-risk women benefit from annual combined mammography and breast MRI screening [335]. Twenty-eight of the OBSP screening sites now offer eligible women high-risk screening services and each of the regions across Ontario has at least one OBSP screening center for high-risk women [2,334].
Screen-eligible women include those aged 30 to 69 years with no acute breast symptoms. These women are considered to be at a high risk of developing breast cancer because they have either a known deleterious BRCA1/2 mutation or another gene mutation that predisposes to a significantly elevated risk of breast cancer; [ii] are a gene mutation carrier’s untested first-degree relative; [iii] have a family history that suggests the presence of hereditary breast cancer syndrome and have a personal lifetime breast cancer risk ≥25%; [iv] have a history of therapeutic chest irradiation [where radiation was received at <30 years of age and at ≥8 years in the past] [93]. In 2011, approximately 34,000 women in Ontario [<1%] became eligible for screening based on these criteria and it is assumed that 17 cancers per year will be detected for every 1,000 high-risk screens performed by this high-risk program [2,334]. The year 1 OBSP high-risk screening program results suggested that an annual MRI in combination with mammography may be an effective strategy for early detection in high-risk women, especially those who are BRCA mutation carriers. Thirty-five cancers were detected at the initial screening. None were detected using only mammography, while 23 [65.7%] were detected using only MRI, and 12 [34.3%] were detected by both MRI and mammography. Twenty-five [71.0%] breast cancers were detected in women known to have BRCA mutations [97]. Combined use of MRI and mammography resulted in the greatest positive predictive value [12.4%].

2.3.2 Breast cancer screening potential harm

Mammography screening of women aged 40–49 years and 50–74 years contributes to statistically significant reductions in breast cancer specific mortality [336]. However, the potential harms associated with screening for breast cancer must also be addressed. The balance between the benefits and potential harms of breast cancer screening is a topic of much controversy and debate. The issue of over diagnosis is central to this debate. Over-diagnosis of breast cancer refers to finding cancers that would never have been clinically apparent during a woman’s lifetime without the intervention of screening. Because there
is no method to distinguish between cancers that would never be symptomatic and cancers that would lead to death if left untreated, both types are treated similarly. Thus, treatment of an over-diagnosed cancer subjects a woman to the harms of cancer treatment without a therapeutic benefit [337]. While it is difficult to quantify the magnitude of over-diagnosis, estimates range from 0% to >50% because of major differences between populations, cancer types, and estimation methods [337,338]. The most robust method to estimate over-diagnosis is to compare cumulative breast cancer incidence in the screened and unscreened groups of a randomized controlled trial [RCT] in which there are adequate years of follow-up after screening ends and in which the control group was never screened [339]. The results of two reviews [Pace & Keating [337] and Marmot et al. [338]] suggest that this question of over-diagnosis could be addressed based on the evidence gleaned from the long-term follow-ups of three RCTs [i.e., the Malmo I trial [340] and the Canadian National Breast Screening Study trials [341,342]], where the investigators never invited the control groups to be screened. The results of a meta-analysis of these trials looking at the over-diagnosis estimates indicated that 10.7% of breast cancers were over-diagnosed in women invited for screening mammography [343].

A false-positive breast cancer screening result refers to a positive or abnormal result on a screening test that is subsequently found not to be cancer during recall for further assessment. Women <50 years of age are more likely to have a false-positive result [344]. Harms from a false-positive result include undergoing unnecessary diagnostic procedures [e.g., additional mammograms or other imaging tests, fine-needle aspiration, or open biopsy] and psychological distress [345]. A recent systematic review found that having a false-positive mammogram result is associated with psychological distress that persists for up to three years, that distress increases with the level of invasiveness of the diagnostic procedure, and that women are significantly less likely to return for the next round of screening [345].

Moderate- and high-dose chest irradiation is a risk factor for greater breast cancer incidence and breast cancer-specific mortality. The greatest risk is associated with chest wall radiation exposure before 20 years of age [346,347]. The radiation dose from a standard two-view mammogram is very low. The risks of radiation-induced breast cancer
are likely outweighed by the reduction in mortality achievable with annual or biennial screening mammography for women \( \geq 40 \) years of age [348], but regular exposure to low-dose chest irradiation starting at a young age might increase the lifetime risk. Mammography screening begins as young as 25-30 years of age in women with a first-degree family history of breast or ovarian cancer, or both, who are known or suspected to be BRCA mutation carriers. It has been hypothesized that carriers of BRCA mutations have increased radio-sensitivity due to an impaired response to double strand DNA breaks, which can be caused by ionizing radiation [349]. Millikan et al. found a significant positive association between breast cancer and the lifetime number of mammograms in genetically predisposed women [350]. Results reported by Pijpe et al. suggest that mammogram use before 30 years of age increases the risk of breast cancer in women who are carriers of BRCA1 or BRCA2 mutations [351]. The results of other studies indicated there is no increased risk for these women [352-354]. Much of the evidence regarding breast cancer risk associated with diagnostic and screening mammography comes from studies that include screen-film mammography. The average radiation dose from digital mammography is approximately 20% lower than that from screen-film mammography [4.7 mGy for a standard two-view screen-film mammogram versus 3.7 mGy for a digital mammogram] [355]. Given that the use of digital mammography is increasing, the risks of breast cancers felt to be mammography-induced in the future may be lower than those reported by previous studies.

2.3.3 Participation in breast cancer screening

The 2008 Canadian Community Health Survey [CCHS] found that 72.5% of Canadian women 50–69 years of age self-reported undergoing a mammogram in the previous 2 years [356]. While this result represented a significant increase from the 40.5% of women who reported having a mammogram in 1990, all this increase occurred during 1990–2001. Self-reported rates from 2001–2008 remained stable at approximately 72% [356]. In Ontario, self-reported mammogram participation during the previous 2 years was
73.2% in 2008, down slightly from 73.6% in 2000–2001 [356]. These self-reported participation rates do not distinguish between screening and diagnostic examinations, but 91% of the 2008 CCHS respondents reported that their mammogram was for screening purposes [356].

Epidemiologic research relies heavily on self-reported mammography data to determine rates of screening participation. Study results indicate that the use of self-reported mammography data is a valid approach [355-359]. Evidence from meta-analyses indicates that self-reported data performs well in terms of accuracy when evaluating whether a woman has had a mammogram, and the sensitivity rates exceed 90% [357-359]. However, self-reported data is much less accurate at determining the exact time of mammography use [357-367]. Studies have consistently found that the time since the last mammogram is often underestimated by women [357-367]. This phenomenon, ‘telescoping’, occurs when an individual recalls an event as more recent than it was [368]. In the case of mammography, the effect of telescoping results in an over-estimation of mammogram use and inflates rates of screening adherence. Some studies have found that age, ethnicity, income, education, marital status, indication for a mammogram, recency of a mammogram, and a family history of breast cancer are all associated with the accuracy of self-reported mammogram data. Other studies have found no evidence that factors such as age, income, ethnicity, perceived risk, or number of years since the last visit to a health professional are significantly associated with recall [361-375]. The quality of self-reported mammogram use data has been examined in depth, but studies have focused on women who have a population-level breast cancer risk. The two studies that validated the use of self-reported mammogram data in women with a familial risk only included those with very strong familial breast cancer histories [376,377]. Compared with women in the general population with familial risk, these women were likely to have different breast cancer screening behaviors and recall of these behaviors.

Results of analyses of Ontario Health Insurance Plan (OHIP) and OBSP data indicate that participation in mammography screening in Ontario is lower than suggested by the results of analyses of self-reported data from the CCHS. In 2010–2011, 60.8% of eligible women in Ontario were screened using mammography. This rate was similar to the
2008–2009 result, when 61.1% of eligible women in the province were screened using mammography [335]. However, these rates were slightly lower than the 2007–2008 result, when an estimated 66.3% of eligible average-risk women were screened, and lower again than the 64.0% in 2005–2006 and 61.5% seen in both 2003–2004 and 2001–2002 [335]. The current screening mammography participation rate in Ontario is currently below the national target of 70% [335]. Most screening mammograms performed in Ontario occur within the context of the OBSP where, in 2010–2011, 71.1% of screening mammograms were performed at an OBSP site [335]. This result represents an increase from 2008–2009, when 65.7% of women were screened within the OBSP [335], therefore it is possible that OBSP data under-estimates the screening rates that would be calculated if all screening mammograms could be data captured.

2.3.4 High-risk breast cancer screening

A 19-study meta-analysis found a positive association between a family history of breast cancer and mammogram use. Compared with women without a family history of breast cancer, women with a familial risk were more likely to undergo mammography screening [Pearson’s r = 0.27, p < 0.001] [378]. However, many of these studies examined whether screening mammography was ever used instead of its use as part of a guideline-adherent screening interval. The results of several subsequent studies in women with a familial breast cancer risk [e.g., BRCA1/2 mutation carriers, attendance at genetic counseling], have suggested that these women have relatively high rates of mammography adherence [67–90%] and CBE guideline adherence [379-382]. One Australian and two North-American population-based studies of women with family histories of breast cancer in multiple of their family members, found high adherence [74%] and lower levels of adherence, respectively, when compared to mammography guideline recommendations [383-385]. One study found that that during the previous 11 months, only 40% of women in North America had a mammogram [384]. The results of another study indicated that 36.1% of average risk women and 55.5% of moderate to high risk women had a mammogram within the last 12 months [394]. One hypothesis to explain this finding is that the inverted u-shaped curve can be used to represent breast cancer risk. When
compared with women at moderate levels of breast cancer risk, women at the extreme ends of risk due to family history may be complying with screening recommendations at lower rates [386]. This pattern might be mediated by fear of a cancer diagnosis [387,388].

2.4 Breast cancer risk reduction techniques

2.4.1 Risk reduction mastectomy

The use of risk reduction mastectomy for high-risk women is controversial. It presents a difficult decision for the women at risk and a clinical dilemma for health-care providers. PM has also been used for women with extremely painful breasts, with a strong family history of breast cancer, women who have had breast biopsies, and women with “cancerphobia” [389].

The interest in PM as a viable option for risk reduction has increased as the availability of BRCA1/2 mutation testing has increased, but the indications for use of PM remain unclear [390,391]. Results of studies have suggested that risk can be significantly reduced using surgery, but complete prophylaxis might not be achieved [32]. The results of two studies performed in Denmark [392,393] suggested that breast cancer risk can be reduced by up to 50% when a large volume of breast tissue is removed. The survival benefits achieved with the use of surgery for risk reduction in BRCA1/2 mutation carriers have been assessed using decision analysis [394,395]. Survival data from the SEER database and cumulative breast cancer incidence rates [293,396] were used to construct survival models for a simulated cohort of 30-year-old women who were BRCA1/2 mutation carriers. Eighty-five percent [394] and 90% [395] reductions in risk from PM use were included in the model assumptions. Three estimates of breast cancer risk used in these models, which ranged from 40%–85%. The results indicated that PM conferred a life expectancy increase at every risk level [i.e., 2.9–5.3 years [394] and 2.8–3.4 years [395] of increased survival time]. Life expectancy gains decreased as the age of the woman at
the time of surgery increased; women ≥60 years age had minimal gains [394]. Taken together, the results of these modeling studies suggest that PM does confer a survival advantage.

The value of PM for risk reduction has also been measured more directly using retrospective studies of incidence and survival data from women who underwent PM [32,396]. Pennisi and colleagues [396] used a database started in the mid-1970s, where 165 plastic surgeons who were members of the American Board of Plastic Surgery contributed patient information to the database. They examined a group of 1,500 women who were followed for an average of 9 years after subcutaneous mastectomy. In this cohort, six women developed breast cancer. Estimates of the expected numbers of breast cancers and the degree of risk reduction as a result of mastectomy were not included. The study’s limitations included a 30% loss to follow-up, possible biased selection of patients who had favorable outcomes, no defined breast cancer risk, and no central pathology review.

Hartmann and colleagues [32] examined data from a group of 639 women with a family history of breast cancer who had PM during 1960–1993 and were contacted after being identified. Each woman was classified as high [n = 214] or moderate [n = 425] risk based on family history. Women with family histories that suggested the presence of an autosomal-dominant predisposition to breast cancer were classified as being at high-risk. Women with family histories that did not include any high-risk criteria were classified as being at moderate-risk. Between 2 and 25 years after risk reducing mastectomy [RRM], 4 moderate-risk women and 3 high-risk women developed breast cancer [32].

Hartmann and colleagues used two methods to estimate the expected number of breast cancers cases that would have occurred if no PM surgeries had been performed. In the group of women at moderate-risk with a median follow-up time of 14 years, the Gail model [103] predicted that 37.4 breast cancers would occur. There were four cases of breast cancer that actually occurred during that period, resulting in a risk reduction benefit of PM was 89.5%. A sister control group was included in the analysis because the Gail model can under-estimate the risk in women with strong family histories of breast
cancer. The expected number of breast cancer cases in women at high-risk were calculated for this control group, and 30–53 expected cases were estimated by the model, depending on the statistical approach used. There were actually three cases of breast cancer that developed in this cohort, with the risk reduction of 90%–94.3%. The numbers of deaths from breast cancer were reduced in both groups [103].

None of the 18 women in the PM surgery cohort with known deleterious BRCA1/2 mutations or of the 8 women who had mutations of uncertain clinical significance developed breast cancer [398]. The results of using the Easton [395] and Struewing [293] penetrance models to estimate the level of risk reduction indicated that the risk reduction was statistically significant. Breast cancer occurred in 3 of the 214 high-risk women, where 2 of these women had a known mutation status, but neither had a BRCA1 or BRCA2 mutation. PM effectiveness among BRCA1/2 carriers was calculated two ways: first, including the assumption that the patient with unknown mutation status was a carrier and, second, including the assumption that she was not a carrier. The results indicated that with either assumption, the risk reduction was approximately 90%.

A study of a Dutch population [275] estimated PM-associated risk reduction in 76 carriers of BRCA1/2 mutations. Without PM, six cases of breast cancer would have been expected during the median follow-up time of 2.8 months.

Taken together, these study results indicate that prophylactic removal of a substantial amount of breast tissue results in a decreased risk of breast cancer in women at high-risk for the disease; PM might also reduce the risk for women with BRCA1/2 mutations. The limited amount of information about the patients' actual level of risk [32] and the brief follow-up interval used [275] limit the results of these studies. A non-randomized prospective trial of women at defined levels of risk likely could be performed to obtain high-quality data if physicians had clinical equipoise regarding the perceived benefit of PM, however, the use of PM for risk reduction is supported by these results.

The perceptions by women regarding PM when the women have not undergone genetic testing but have an increased breast cancer risk related to family history or breast pathology, or both, have been investigated [399,400,382,401]. A study of French women
visiting, or waiting for an initial appointment at, cancer genetic clinics revealed that 20.3% \( [n = 473] \) of women agreed that PM was an acceptable option for women who have BRCA1/2 mutations. However, only 4.7% agreed that PM was reasonable option for women <35 years of age. Meiser and colleagues [382] surveyed a population of 333 women visiting, or waiting for an initial appointment at, cancer genetic clinics. Nineteen percent responded that they would consider PM if they had a BRCA1/2 mutation, while 54% were unsure. A woman’s age, personal risk estimate value, and degree of anxiety about breast cancer correlated with the response about PM. Women with a high personal risk estimate, who were younger, and who had higher levels of anxiety about breast cancer were more likely to respond that they would consider PM.

Two studies used a vignette approach to examine perceptions regarding PM among women in the United States [399, 401]. A clinical scenario that involved a woman with an increased risk of breast cancer was presented to the study participants. They were instructed to view themselves in the same position and select from options for follow-up. The study completed by Stefanek and colleagues [401] included a population of unaffected women who had \( [n = 129] \) or did not have \( [n = 104] \) a family history of breast cancer. The results of this study were consistent with the previously described studies. The only alternative follow-up option to PM offered to these women was surveillance [i.e., annual mammograms starting at a young age, three times per year CBE, and monthly breast self-examination]. PM was selected by approximately 25% of the women. There were no differences in PM selection by the women who did [29.5%], and did not have[22.1%] a family history of breast cancer. Anxiety about breast cancer and the personal risk estimate were statistically significant predictors of PM choice. Eighty-two percent of the women in the study population agreed that surgery should be discussed as an option for women at increased risk.

Geller and colleagues [399] used a vignette format during a survey of 426 unaffected women, where each woman had a family history of breast cancer. Five percent responded that they would be likely or very likely to agree to undergo PM if they had a positive test result for BRCA1/2 mutation. Compared with the previous studies, the PM acceptability rate estimate in this study was much lower. Between-study differences in vignette
content, the instructional sets, or the population cultural attitudes and beliefs of the populations might account for this difference [402], as well as social media and cultural acceptance of PM in terms of body image perceptions among women changing over time with increased uptake among well-known celebrities.

Perception of PM among BRCA1/2 mutation carriers has also been examined [34,403,453]. In one study of 13 BRCA1/2 carriers in Austria without any personal history of breast cancer, the investigators found that at 5 months after disclosure of test results, 8% [1/13] of these carriers certainly would or would be likely to consent to PM [403]. Lerman and colleagues [404] found that during the 12 months after testing, 3% [1/29] of unaffected BRCA1/2 mutation carriers underwent RRM.

At least one study has reported findings that are inconsistent with these findings. A study performed at the Rotterdam Family Cancer Clinic [275] found that 55% [76/139] of women with BRCA1/2 mutation chose PM. However, these women were not offered the option of chemoprevention, and may have been referred to this center specifically because they were seeking PM as a risk-reducing intervention.

The ability to make definitive conclusions about the perceptions of at-risk women about PM is affected by between-study differences in study design and unexamined risk factors. Some investigators inquired about preferences for follow-up, while others used a vignette format. Small sample sizes were used in the few studies that examined carriers of BRCA1/2 mutations. Compared with other studies, the study published by Meijers-Heijboer and colleagues [275] found that a much larger proportion of women selected surgery. Differences in culture, health-care services delivery systems, the medical specialties involved in the discussions about follow-up options, or in the type of follow-up information provided may have contributed to differences in study findings [402]. Overall, the risk and benefit information about PM that was provided to the study participants was not adequately described in these publications. The type of information provided could absolutely substantially influence the perception of benefit for PM among high-risk women. However, the studies did support the recommendation that the PM option should be discussed with women at an increased breast cancer risk.
2.4.1.1. Prophylactic mastectomy

Enhanced screening, chemoprevention, and risk-reducing surgery are the options presented to women at elevated risk of breast cancer due to gene mutations or a strong family history of breast cancer. Total or subcutaneous BPM is used for women who select risk-reducing surgery because BPM is the most effective surgical method for cancer risk reduction. Use of BPM also reduces the risk by approximately 90% in BRCA1/2 mutation carriers [405].

Mailed surveys were used to examine the effects of BPM on characteristics associated with long-term quality of life (QOL) [406]. The surveys were sent to 195 women who underwent BPM between 1979–1999. They were also sent to 117 randomly-selected women at increased breast cancer risk who did not have BPM. The survey included validated measures of body image, QOL, breast cancer apprehension, sexuality, health perception, depression, and demographic characteristics. Logistic regression analysis was used to examine associations between QOL and other domains. The response rate for completed surveys was 58%, which included 106 women who had BPM and 62 women who did not have BPMs. Eighty-four percent of the women who underwent BPM were satisfied with their decision to have the procedure. Sixty-one percent of these women reported high contentment with QOL, compared to an identical 61% of those who did not have BPM [P = 1.0]. Among all participants, diminished contentment with QOL was associated with dissatisfaction with sex life [adjusted odds ratio [OR]: 2.5, 95% CI: 1.0–6.2], possible depression [CES-D > 16, OR: 4.9, CI: 2.0–11.8], and a poor or fair general health perception [OR: 8.3, 95% CI: 2.4–29.0]. Most women responded that they were satisfied with BPM and had psychosocial outcomes no different from women with a similarly elevated breast cancer risk who did not undergo BPM [406].

Risk factors that predict QOL were examined in women in Ontario, Canada who underwent BPM between 1991–2000 [407]. The survey questions were used to assess
metrics that measure current psychosocial functioning [e.g., Quality of Life Index (QLI)]. The results indicated that the mean QLI score value was 23.34 [range 9.53–30.00]. There were statistically significant negative correlations between mean QLI score and psychological distress, cancer-related distress, and worries about body image, while there was a statistically significant positive correlation between QLI score and level of social support. Psychological distress and the vulnerability component on the body image subscale were statistically significant predictors of QOL [407].

Compared with BPM, little is known about the psychosocial outcomes for women who choose contralateral prophylactic mastectomy (CPM). CPM is a risk-reducing mastectomy performed in patient who are at elevated risk of developing a contralateral breast cancer (such as patients with lobular carcinoma in situ of the affected breast, or who have significant anxiety with the thought of having annual screening of the contralateral breast and don’t want to accept the low risk of a new contralateral breast cancer in the future). Results of quantitative, closed-ended format surveys indicate that a large proportion of women who undergo PM are satisfied with their decision to choose the procedure [408]. The components of this response were assessed using questions with a qualitative, open-ended format. The open-ended questions were included in a mailed survey of the psychosocial outcomes of PM. Qualitative methods were used to code and analyze the responses. The demographics of the entire surveyed population were compared to the demographics of the women who answered the open-ended questions using simple descriptive statistics to analyze the responses. The responses to the closed- and open-ended satisfaction questions were compared, and between-group comparisons of the responses of women with BPM versus contralateral prophylactic mastectomy CPM were performed. Of the 71% of women with BPM who responded to the survey, 48% answered all the open-ended psychosocial outcome-related questions. The responses were coded as positive, negative, or disparate. In the subgroup of women with both open- and closed-ended responses, over 70% of women providing negative and disparate comments to the open-ended question simultaneously indicated satisfaction on a closed-ended question. Negative and disparate open-ended responses were twice as common among women with BPM [52%] than women with CPM [26%] [408].
BPM reduces the risk of breast cancer development by approximately 90%. More women at high-risk are choosing BPM as part of a strategy to reduce risk. This may be related to increased visibility of this option among well-known celebrities such as Angelina Jolie and is possibly also related to improved access to immediate breast reconstruction over time. Reconstructive breast surgery is frequently part of the immediate treatment plan. Breast reconstruction has important emotional and physiological effects on QOL, body image, and sexuality. Before surgery, the type of mastectomy planned, the timing of the reconstructive surgery, the availability or appropriateness of all reconstruction options, and potential preservation of the NAC must be discussed with the patient [409].

Since the early 1990s, Karolinska University Hospital [Sweden] medical teams have performed BPM as a risk reduction method for women with a familial risk for breast or ovarian cancer, or both. Short-term follow-up evaluations [1–3 years] were used to investigate the perceptions of the women who underwent these procedures [410]. The 10-year long-term physical and psychological consequences of BPM was also examined in this cohort. Thirteen of these women responded to semi-structured interviews about their long-term experience with the consequences of BPM and immediate breast reconstruction (IBR). The results indicated that the respondents thought that they had a negligible risk of breast cancer and were satisfied with the decision to choose BPM. For most women, BPM did not affect lifestyle or family life [n=8/13], and the cosmetic results were mostly positive [n=10]. Eight women responded that BPM had positive [n=3] or negative [n=5] effects on their relationship with their spouse [410].

Aesthetic and long-term oncologic outcomes, complications, and patient satisfaction of were examined using a retrospective study of a 25-year period during which patients underwent the procedure [511]. Forty of 52 patients had CPM; 12 had BPM [i.e., 64 breasts removed]; 1.56% [1/64] of the mastectomy specimens contained breast cancer cells. Subcutaneous PM was performed in 65.62% [42/64] and simple total PM was performed in 34.37% [22/64] of the breasts. Alloplastics were used for reconstruction of 90.62% [58/64] of the breasts; autologous tissue was used for 9.37% [6/64] of the breasts. Five breasts [7.81%] received a latissimus dorsi flap with an alloplastic implant; 1 [1.56%] breast had a TRAM flap. Post-surgery, capsular contracture occurred in 6.25%
breasts, 3.12% [2/64] breasts developed a hematoma, and infection occurred in 1 [1.56%] breast. Seventy-five percent [39/52] of the patients reported being highly satisfied, 19.23% [10/52] reported being partially satisfied, and 5.76% [3/52] reported being unsatisfied with the outcome [411]. The objectives of one systematic review were to identify studies of health-related QOL [HRQOL] in patients after BPM [with or without reconstruction], assess the effects of BPM in these patients, and identify predictors of post-BPM HRQOL characteristics. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, the investigators performed a systematic literature review that included a search of the Embase, PubMed, Web of Science, PsycINFO, Cochrane, and Scopus databases [512]. A total of 1,082 studies were found by the initial search, and 22 studies met the inclusion criteria. The review results indicated after BPM, women were satisfied with the outcomes, had high psychosocial well-being, and a positive body image. BPM had the greatest negative effects on somatosensory function and sexual well-being. Pre-operative cancer distress, psychological distress, and vulnerability were statistically significant negative predictors of post-BPM QOL and body image. The researchers concluded that more high-quality data on outcomes of different post-BPM HRQOL domains are needed, and that validated and breast-specific patient-reported outcome instruments should be used to measure HRQOL. Use of this approach should allow surgeons to provided evidence-based information to patients and improve the outcomes of shared decision-making [412].

A prospectively maintained database was used to examine the factors that can affect decision making in a study of a group of BRCA mutation carriers who chose BPM, compared with carriers who chose surveillance [513]. The surveillance cohort [n = 313] consisted of high-risk clinic patients examined between 2014–2016, while the surgery cohort [n = 142] consisted of women who had BPM between 2010–2016. The results for a between-group [i.e., BPM versus surveillance group] comparison of clinical and familial factors indicated that the women who chose BPM were more likely to have a BRCA1 mutation than a BRCA2 mutation, compared with the surveillance group [57% versus 45%, p = 0.02]. They were also less likely to have a personal history of ovarian cancer [10% versus 20%, p = 0.01]. It is reasonable to expect that this reflects the prognosis for patients with ovarian cancer and the significant 5 year mortality which
would deter patients from engaging in prophylactic surgery if it were not going to impact on their survival. The women who underwent BPM were more likely to be married [78% versus 62%, p = 0.01], and to have more children [median 2 versus 1, p < 0.001]. The women who chose BPM had more first-degree relatives [63 versus 48%, p = 0.01] or a sister [23 versus 14%, p = 0.02] with a history of breast cancer, and they were more likely to have a family member with ovarian cancer <40 years of age [9% versus 4%, p = 0.03]. The between-group differences in the numbers of previous breast biopsies or in rates of personal history of atypia/lobular carcinoma in situ were not statistically significant. The researchers concluded that the decision to have a BPM is multifactorial; gene mutation, family history, and relationships have the strongest effects during the decision-making process [413].

2.4.1.2 Breast cancer risk after prophylactic mastectomy

Use of surgery to reduce risk of breast cancer is an effective option for women at high-risk for breast cancer [414]. Bilateral mastectomy can reduce the risk of breast cancer by approximately 90% [32]. The remaining risk is presumably related to the residual mammary gland epithelial tissue that remains after surgery. The two techniques, SSM with or without nipple-sparing and total mastectomy have the potential to leave different amounts of mammary gland tissue. During nipple-sparing SSM, a small amount of the sub-areolar breast epithelium remains after the subcutaneous mastectomy is completed [415]. Study results indicate that overall, 0.2%–1% of patients who undergo BPM develop invasive breast cancer [416]. However, higher rates have been reported where breast cancer occurred after BPM in 1% [six cases] and 19% [three cases] of high-risk women [416-417].

Hartmann and colleagues [420] examined a cohort of 1,125 women who underwent BPM and completed a questionnaire that asked about family history of breast cancer. A family history was reported by 580 respondents where 203 had a family history that suggested
that they had a single-gene inherited risk. During the mean 17-year follow-up, 7 women developed breast cancer; 5 of the cases were in women who reported having a family history. Compared with Gail model risk analysis and age-adjusted SEER incidence rate results, the breast cancer risk reduction was 91% [420].

Therefore, PM markedly decreases the risk, but does not eliminate the possibility of new breast cancer in the residual breast tissue, axilla, or chest wall on the PM side [421]. During long-term follow-up of 1,065 women who underwent BPM and 1,643 women who had CPM for contralateral breast cancer, 25 women developed locoregional, invasive breast ipsilateral to the PM. Little has been published on the development of breast cancer after PM because it is a relatively rare clinical entity. Mutter and colleagues [421] published a study in a population of patients felt to represent the largest population to be followed for development of breast cancer after PM. The authors include details about the most common presentations, treatment, pathology, and outcomes. Their results indicate that use of PM [subcutaneous and total] results in a high-level of risk reduction. Consistent with these results and the results from other cohort studies [422], the breast cancer risk reduction is estimated to be 94%–95% when bilateral risk reduction mastectomy (RRM) is used [421,422]. Although studies have indicated that overall risk reduction rates of >90% can be achieved using PM, many studies were not done in gene mutation carriers exclusively.

The studies by Pennisi and Capozzi [419] and Woods [418], as well as others, reported that a few out of >1,000 patients in their studies of prophylactic mastectomy developed breast cancer after years of follow-up [incidence, 0.6%]. Yet, nipple sparing mastectomy (NSM) raises some major concerns. One concern had been that when it is used for prophylaxis, it could theoretically pose a persistent risk of developing breast cancer. There was also controversy in terms of the oncological perspective regarding the safety of such procedures [423,424] but this has been resolved with recent guideline publications [335]. BPM decreases breast cancer risk by >90% [32]. Vulnerability to cancer-specific worry is often found with women who have consistently estimated that they have a breast cancer risk greater than it is [425]. This situation might push women
who are not at very high risk to take unusual measures against breast cancer, including having a BPM.

Rebbeck and colleagues [405] examined a population of 483 women with BRCA1/2 mutations. Two [1.9\%] of the 105 women who had BPM and 184 [48.7\%] of the 378 matched controls [no surgery] had a diagnosis of breast cancer during the mean follow-up of 6.4 years. The authors concluded that use of BPM results in an approximately 90\% reduction in breast cancer risk in women with BRCA1/2 mutations. A prospective study of 139 women with BRCA1/2 mutations found that breast cancer developed in 8 of 63 women who chose surveillance; none of the 76 carriers who chose prophylactic surgery developed breast cancer [405].

There are few studies that describe the mammographic and sonographic appearance of breast cancer when it occurs in BRCA-positive patients' reconstructed breasts. The morphologic features of post-PM tumors in BRCA1 and BRCA2 mutation carriers include the presence of continuous pushing margins [223]. Because there is reduced potential for stromal infiltration, the tumor’s appearance on the mammographic and sonographic images might mimic the appearance of a benign lesion [426].

Risk-reducing surgery options for women who are BRCA1/2 gene mutation carriers also include prophylactic bilateral salpingo-oophorectomy in addition to BPM. The survival benefits arising from different treatment options have been studied using the Markov model. Grann and colleagues [395] compared bilateral oophorectomy, bilateral mastectomy, or having both procedures with surveillance alone. They found that compared with surveillance alone, survival of a 30-year-old BRCA1/2-positive woman was increased by 0.9 years [95\% probability interval, 0.4–1.2 years] with bilateral oophorectomy, 3.4 years [2.7–3.7 years] with bilateral mastectomy, and 4.3 years [3.6–4.6 years] with both procedures. The results of this study suggest that significant survival benefits result from the use of prophylactic surgery. The results of other studies indicated that compared with the use of breast and ovarian screening, the average life expectancy gain for 30-year-old carriers in the high-risk category is 11.7 years for combined PM and oophorectomy, 9.5 years for breast-screening and prophylactic oophorectomy, and 4.9
years for PM with ovarian screening. The gains for carriers at medium risk are 6.6 years for combined PM and oophorectomy, 5.3 years for breast-screening and prophylactic oophorectomy, and 4.4 years for PM with ovarian screening. These results indicated that use of combined PM and oophorectomy confers the greatest survival benefit [427]. Prophylactic oophorectomy also appears better at prolonging survival than BPM. The findings by Schrag and colleagues [394] were similar. The results of the study published by Grann and colleagues [395] also suggested that life expectancy gains declined with the age at the time of prophylactic surgery and were found to be minimal for women ≥60 years of age. Oophorectomy could be delayed by up to 10 years with little loss of the life expectancy gain.

2.4.1.3 Skin-sparing prophylactic mastectomy

Prophylactic skin-sparing mastectomy [SSM] or nipple-sparing mastectomy [NSM] is considered standard of care for risk reducing surgery, with NSM increasingly being performed. Researchers investigated whether NAC preservation during NSM increases patient satisfaction in women who had prophylactic bilateral SSM or NSM and immediate implant breast reconstruction between 2002–2012 [428]. NAC sensitivity after NSM was measured. Patient satisfaction and body image were compared between SSM and NSM. The Breast-Q reconstruction questionnaire was used to assess patient satisfaction. Hopwood's body image scale was used to assess body image. Satisfaction with the reconstructed NAC was assessed using a questionnaire designed for the study. In the NSM group, NAC sensitivity was assessed using Semmes Weinstein monofilaments [5-point scale] and was compared with NAC sensitivity in a control group [where no surgery was performed]. There were 25 women [50 SSMs] in the SSM group and 20 women [39 NSMs] in the NSM group. The median follow-up time was 65 months in the SSM group, compared with 27 months in the NSM group. The SSM group had higher Breast-Q scores, compared with the NSM group ["satisfaction with breasts", 66.2 for SSM group versus 56.6 for NSM group, P = 0.06; "satisfaction with outcome", 76.1 for
SSM group versus 61.5 for NSM group, \( P = 0.09 \). The mean body image scale score was 7.1/30 in the SSM group and 9.3/30 in the NSM group \( [P = 0.35] \). There were no statistically significant differences in Breast-Q scores or body image scale scores after adjusting for follow-up. Levels of satisfaction with the reconstructed NAC were similar after SSM and NSM. NAC sensitivity was lower in the NSM group \( [\text{mean score, 1.9; 95\% CI: 1.5–2.3}] \), compared with the control group \( [\text{mean score, 4.7; 95\% CI: 4.6–4.9}] \). The SSM group had greater Breast-Q scores for satisfaction with breasts and with overall outcome \( [428] \), although these patients would have likely had 2 stage reconstruction rather than one-stage reconstruction, which is more challenging in NSM patients compared with SSM and might be responsible for the difference in satisfaction scores.

2.4.2 Chemoprevention

In the United States, tamoxifen is the only medication approved by the US Food and Drug Administration [FDA] for breast cancer risk reduction in high-risk women, which was initially approved in 1998. National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial [BCPT] \( [429] \) results contributed to the approval decision. The trial used a randomized, controlled [placebo] study design, where the study population consisted of \( >13,000 \) women at high breast cancer risk. The results indicated that use of tamoxifen reduced invasive breast cancer risk by 49\% overall and by 44\% for women \(<50\) years of age, while there was a 50\% reduction in the risk of non-invasive breast cancer. The incidence of ER positive tumor was reduced by 69\%, but there were no between-group differences in ER negative tumor incidence. Compared with the placebo group, the group of patients who took the tamoxifen experienced a greater number of serious adverse events [e.g., endometrial cancer, vascular events such as pulmonary embolism, stroke, deep venous thrombosis, and cataracts] \( [430] \). The overall RR value for endometrial cancer was 2.53 \( [95\% \text{ CI: 1.35–4.97}] \) overall, and 1.21 \( [95\% \text{ CI: 0.41–3.60}] \) for women \(<50\) years of age. The RR value for cataracts was 1.14 \( [95\% \text{ CI: 1.14–10.21}] \).
CI: 1.01–1.29] overall and the RR value for pulmonary embolism was 3.01 [95% CI: 1.15–9.27] [429, 431] overall.

2.4.2.1 Breast cancer risk after chemoprevention

Tamoxifen efficacy for reducing the risk of breast cancer risk in women with BRCA1 or BRCA2 mutation remains unclear. This high-risk subgroup might respond to tamoxifen therapy [431], but tamoxifen may not be as effective in this group because 70%–80% of the tumors that develop are ER negative [432]. One case–control study found that the use of adjuvant tamoxifen resulted in a statistically significant reduction in the odds of contralateral breast cancer in women who were mutation carriers [484], although these would have been women whose index cancer was ER positive and therefore the contralateral risk reduction benefit might not be generalizable to the BRCA mutation cohort overall. Women with ER positive disease would have been more likely to be prescribed tamoxifen. The risk reduction estimates included very wide CIs, and there was an increase in the odds of contralateral disease after tamoxifen was taken for >4 years, likely reflecting the overall increased contralateral risk of breast cancer in patients not undergoing CPM.

The conflicting negative results from two European trials have also indicated that questions about tamoxifen use remain to be answered [434, 435]. Optimal dose and treatment duration, and whether tamoxifen use benefits overall health or survival remain to be determined [432, 436]. Ninety-six percent of the BCPT participants were Caucasian, so the findings may not be generalizable to populations of non-Caucasian women. The BCPT participants were not permitted to take hormone-replacement therapy, androgen, or oral contraceptives, so the efficacy of tamoxifen when it is given with hormonal agents was not examined. These agents as well as any medications [such as anxiolytics metabolized by the hepatic CYP2D6 pathway] might interfere with tamoxifen efficacy.
2.5 Breast reconstruction techniques

Patients are not required to have reconstructive surgery with their BPM as this choice is very individual and therefore a portion of patients chose to forego reconstruction after mastectomy, either felt to be related to individual choice or in patients where their overall prognosis is so poor that breast reconstruction is unjustified [437]. The factors that contribute to a patient’s decision to undergo breast reconstruction were examined by Reaby and colleagues [438] and Ng and colleagues [439]. Lack of information about the procedure, feeling reconstruction is unnecessary for physical or emotional well-being, and fear that reconstruction can mask cancer recurrence are reasons given by patients for refusal [438]. The approximately 33% [440] who chose reconstruction in this study did so that they could avoid problematic external prostheses, to improve thei ability to wear a variety of clothing types, to regain their femininity, and to feel “whole” as breast cancer survivors [438]. Compared with patients who did not undergo reconstruction, patients who had the procedure reported better post-surgical social functioning and emotional well-being [440]. Dissatisfaction with the outcome were found to occur when patients had unclear and inaccurate expectations about breast appearance and physical sensations [e.g., the “unnatural feel”, firmness, and lack of movement] after reconstruction [441].

When reconstruction is chosen, the goal is to restore the breast’s appearance and to improve psychological well-being. Reconstruction of the breast mound and the NAC are both addressed during the decision-making process [442]. Implant [alloplastic] and autologous reconstruction are the two main techniques used for breast reconstruction. Implant reconstruction involves the use of an implant filled with saline, silicone gel, or a combination of these. Autologous reconstruction uses a tissue flap [e.g., from the belly, back, or thigh] and might also include use of an implant. Prosthetic breast reconstruction is thought to be a lower-cost procedure, since it is associated with shorter procedure times, hospital stays, and recovery times [443]. The implant-based approach does not require use of a tissue donor site [444]. The factors considered during discussions between the patient and surgeon when deciding between implant or autologous
reconstruction include the patient’s general medical health, breast size and ptosis, areola size, donor site suitability, the patient’s expectations, preferences, smoking status, lifestyle factors, and resource availability. The surgeon’s preferences and experience are also considered.

2.5.1 Prophylactic mastectomy with implant-based reconstruction

Use of implants is the most commonly-used breast reconstruction approach. Approximately 75% of breast reconstructions performed in the United States are implant-based. In most cases, the existing breast reconstruction options are felt to result in a satisfactory outcome [445]. The reconstruction can be performed at the same time as the mastectomy [Immediate Breast Reconstruction, or IBR]. It can also be a two-stage reconstruction consisting of a tissue expander placement, serial inflation in clinic followed by subsequent permanent implant placement in a second surgery [446].

Restoration of mammary volume and shape results in physical and psychological benefits [447]. Therefore, immediate reconstruction is the preferred approach, with a high degree of patient satisfaction felt to be associated with use of immediate reconstruction [448,449]. Disadvantages of the use of prosthetic [implant] IBR include the potential need for additional surgery for reconstruction revision [450,451] and prosthesis failure over a patient’s lifetime [452]. The best candidates for ipsilateral mastectomy and IBR have small, minimally ptotic breasts [453] because larger or ptotic breasts, or both, require the use of contralateral balancing procedures during surgery or as a second procedure, to achieve symmetry, which can be very challenging at the time of IBR [454].
2.5.1.1 One-stage ADM-assisted implant breast reconstruction

ADM-assisted IBR enables the reconstruction of breasts with varying degrees of ptosis [455]. For the most part, implants used in breast reconstruction are placed beneath two layers of tissue: pectoral muscle and breast skin. In patients wishing one stage implant-based reconstruction during their mastectomy surgery, the pectoral muscle is too tight and short to permit full muscle coverage of the implant, therefore ADM can be used as a pectoral expander to cover the inferolateral pole of the implant and prevent the need for elevation of the surrounding serratus muscle, thus reducing postoperative pain [456-458]. ADM can also be used as an internal sling to completely cover the implant during subcutaneous breast reconstruction, anchoring the implant to the chest wall without elevating pectoralis, yet providing an additional layer of tissue support, an emerging potential method of implant-based reconstruction being explored by some plastic reconstructive surgeons [459-461].

The use of ADM is felt to provide the reconstructed breast with a natural shape, a well-defined inframammary fold, and enhanced inferior pole projection that is a better match to the contralateral native breast [462]. Characteristics of the breast soft tissue and skin elasticity of the trunk and overall body habitus are typically evaluated before surgery [463] to optimize the changes of a natural appearing reconstruction.

A well-vascularized mastectomy skin flap with a reasonably thick subcutaneous layer is essential for a successful outcome [463, 464]. The intra-operative judgment of the surgeon is the single most important factor that affects the success of direct-to-implant IBR [465-467]. Only patients with good-quality mastectomy flaps [thick and well-vascularized] should be candidates for IBR to minimize the chance of mastectomy flap necrosis [462]. Intra-operative objective assessment tools such as real-time perfusion mapping [e.g., SPY®, Novadaq Technologies Inc., Bonita Springs, FL, USA] can assist surgeons during this key decision-making stage [468].
2.5.1.2 Two-stage ADM-assisted TE-Implant-based breast reconstruction

Like single-stage implant IBR, two-stage tissue expander/implant-based reconstruction aims to create a naturally appearing breast mound. The two stages of surgery are separated by a period to allow for gradual expansion, without compromising the mastectomy flap blood supply. The skin flaps are inspected after mastectomy, and tissue expanders are placed in a sub-pectoral pocket, which is filled to the tolerated volume [10%–50% of the total volume]. The expansion procedure begins during days 10–14 after surgery, where 60–120 ml fluid is added at each visit. The objectives include achieving adequate ptosis and formation of a well-defined inframammary fold. The projected final breast size and other objectives are usually achieved at the fifth or sixth visit. When expansion is completed, final exchange can take place.

The total period for expansion and overall impact on patients can be reduced by maximizing expansion volumes and minimizing the number of expansions. It is also beneficial to fill the expander with as much fluid as possible during surgery. A poor-quality skin flap, previous radiotherapy, and an excessively tight skin or muscular envelope are contraindications for the use of accelerated expansion. Experienced physicians develop clinical judgment that is invaluable for decision-making during this process.

2.5.1.3 One stage dermal sling (non-ADM)-assisted implant-based breast reconstruction

Breast reconstruction can be performed using simple implant-based or more complex myocutaneous flap procedures. One often-used option for implant or tissue expander breast reconstruction is superior placement of the pectoral muscle and inferolateral placement of the biological material [457,469, 470]. During bilateral reconstruction, well-
contoured, symmetrical breasts can be created in some patients with a redundant breast skin envelope using the lower portion of the skin as a dermal sling [lower pole skin is de-epithelialized to create a vascularized local dermal flap] in an inferior position to completely cover the implant or tissue expander and create a tension-free sub-muscular pocket [471-473]. A de-epithelialized vascularized flap covers the lower portion of the implant or tissue expander, which allows for local wound care during a superficial skin infection or skin necrosis. There are many variations in terminology and technique, but most surgeons use an anchor-shaped reduction incision or a transverse non-nipple sparing incision across the breast along with the lower dermal de-epithelialized flap sling for coverage of the lower pole.

2.5.1.4 Two stages traditional TE-Implant based breast reconstruction

Traditional TE/implant-based reconstruction is one of breast reconstruction technique that can be performed without using ADM or Inferior dermal sling, as a two-stages procedure either immediately at the time of the mastectomy or delayed. During the first stage and after mastectomy, a complete sub muscular pocket is created for the TE by elevating the pectoralis major muscle and the anterior insertion of the anterior serratus muscle. In The second stage once the desired breast expansion is achieved, TE-implant exchange is performed.

2.5.2 Prophylactic mastectomy with autologous-based reconstruction

Ptosis, texture, and flexible response to body weight fluctuation are superior late cosmetic results associated with autologous tissue breast reconstruction, compared with implant-based reconstruction. Lower abdomen deep inferior epigastric perforator [DIEP] and
transverse rectus abdominus myocutaneous [TRAM] flaps are the more commonly used of the options available for autologous tissue reconstruction [474].

2.5.2.1 One-stage autologous breast reconstruction

Adequate volume, a reliable blood supply, and excellent aesthetic results are achieved when lower abdominal skin flaps are used [475]. The transabdominal muscle flap (TRAM) [476] can be used as a local pedicle or a free tissue transfer flap [477]. Drucker-Zertuche and colleagues [478] compared 85 patients who underwent TRAM, implant-based, or latissimus dorsi reconstruction. They found that the patients who had TRAM flap reconstruction had more natural breast consistency and mobility [478]. TRAM flap patients also report higher levels of satisfaction with the aesthetic result [479]. TRAM flap reconstruction is associated with donor site complications [e.g., weakness of the abdominal wall] and bulging at the lower inner part of the breast. Therefore, its use has mostly been replaced by the use of the abdominal wall-origin muscle-sparing free flap [e.g., Deep inferior epigastric perforator flap (DIEP)].

Compared with the TRAM flap, the DIEP flap [480,481] has donor site advantages and allows transfer of larger volumes of tissue. Rates of post-surgical complications [e.g., asymmetry, muscular weakness, bulging, and hernia] are reduced because the total abdominal musculature and aponeurotic layers are preserved [482]. Compared with the TRAM flap, during the DIEP flap and superficial inferior epigastric artery flap procedures, the same amounts of tissue are transferred from the abdomen, but the rectus muscle and fascia are unaffected [442]. Like the native breast, the new breast is mostly fat and skin, and patients have a more realistic abdominal contour. The DIEP flap procedure requires a high degree of technical skill. Because SSM allows limited surgical access, identification and dissection of recipient-site vessels can be challenging and incisions are usually extended to allow for access to vessels for anastomosis [internal mammary or lateral thoracic].
The results of a review of 30 DIEP flap surgeries [average follow-up, 29 months] found that during the follow-up period, small areas of necrosis developed on the breast skin of 2 patients. Two patients had partial flap loss that consisted of <15% of the total flap area. One patient experienced total flap loss and one had local breast cancer recurrence. High-levels of satisfaction with the outcome were reported by the patients [483]. Another study compared DIEP flap SSM and IBR with breast conservation. Use of the DIEP flap was associated with a statistically significant better cosmetic outcome and comparable QOL outcomes among the study population of 42 patients [484]. Fujino and colleagues [485] suggested the use of a free flap of soft tissue from the gluteal region. Allen and Tucker [486] used a free superior-gluteal artery perforator flap. Free transfer of skin and fat without loss of the gluteus maximus and minimal donor site complications are advantages of this technique. Limited sensory nerve function can sometimes be achieved when nerves included in the flap are connected to local branches at the recipient site [481]. This method can be used when the abdomen is not a suitable donor site. A study of 142 women who underwent the gluteal artery perforator flap procedure found that use of the superior-gluteal artery perforator flap method had statistically significant advantages over use of the inferior-gluteal artery perforator flap. Ninety-eight percent flap survival, low morbidity rates, high patient satisfaction levels, and good cosmetic results were outcomes associated with the use of the superior-gluteal artery perforator flap method [487].

The myocutaneous transverse upper gracilis free flap has also been used for autologous breast reconstruction [488-490]. Jimenez [491] used free omental flaps harvested using laparoscopy for IBR after SSM. During SSM, a myocutaneous flap might allow replacement of a small area of excised skin and replace the approximate total volume of breast tissue removed, with or without a prosthetic implant [491]. Despite these advantages, a survey of female plastic surgeons [n = 453] in the United States and Canada found that 66% would prefer implant-based compared with autologous breast reconstruction if they themselves had breast cancer [492].
2.6 Acellular dermal matrix (ADM)

Human and animal tissues [e.g., pericardium, back dermis, small intestinal submucosa] can all be processed to obtain a biomaterial acellular reconstruction material. ADM is a dermal matrix and therefore human cadavers, porcine, and bovine sources can all be harvested, processed and de-cellularized to be used for ADM. During the processing procedure, which varies between manufacturer of each ADM type, cells are removed by digestive processes, and the extracellular matrix is retained. This cell-free composition distinguishes ADM from the classical xenografts and allografts, where use of animal tissue will typically contain cells from that animal. Harvested ADM is commercially harvested and has been FDA-approved for many clinical uses in humans for over 10 years [Figure 1] [493].

**Figure 1.** Acellular dermal matrix (ADM), This photo provided courtesy of Allergan.
The potential for inflammation or rejection is eliminated during the processing to obtain ADM. The tissue is separated using mechanical methods, then is de-cellularized and disinfected. Some products are dehydrated or lyophilized and sterilized. The ADM architecture [and interaction with host tissue] can be affected by each step in this process [494].

Integration, resorption, and encapsulation are the three main immunological responses to an implanted ADM [495,496]. Successful integration occurs when there is no immunological recognition and the matrix is rapidly revascularized and incorporated into the recipient site. An inflammatory reaction at the ADM/host interface suggests that the material is being resorbed, with resulting breakdown and elimination [Figure 2] [495]. A foreign body reaction results in encapsulation of the ADM with scar tissue. Sandor and colleagues [496] found that encapsulation is more common when a cross-linked matrix ADM product is used.

**Figure 2.** Acellular dermal matrix revascularized and incorporated into the recipient site, This photo provided courtesy of Allergan.
Duncan and colleagues [497] were the first to publish a report for the use of ADM in breast surgery. They used AlloDerm® in a series of 34 patients undergoing revision surgery to their implant reconstructed breasts to correct post-implant rippling. ADM provides surgeons with an alternative method to obtain enough vascularized soft tissue volume to cover the implant and prevent some complications. Breuing and Warren [498] were the first to report results of the use of ADM for reconstructive breast surgery.

Within 10 years after the first report, the use of ADM was included in more than 60% of all alloplastic reconstruction surgeries performed in the United States [Lifecell]. Additional allogenic and xenogenic ADMs are now available, but AlloDerm® has the longest history of use and is the most-studied product [497]. Other ADMs include DermaMatrix [Synthes, USA], Flex HD [Ethicon, USA], SurgiMend [TEI Biosciences, USA], and AlloMax [Bard Davol, USA]. TIGR Matrix [Novus Scientific, USA, absorbable synthetic] mesh and TiMesh [Biomet, USA, titanized] are synthetic non-ADM mesh products. Processing differences result in between-product differences in handling, incorporation, shelf life, and cost. The effects of these variables on outcomes remain to be determined.

2.6.1 The novel application of ADM in immediate breast reconstruction

The use of ADM for implant-based breast reconstruction has potential clinical advantages including post-operative pain reduction, elimination of the need for elevation of the serratus anterior muscle for lateral coverage of the prosthesis, improved lower pole projection, better aesthetic shape, and improved soft tissue characteristics [46,470,499]. Other reported clinical benefits of ADM include making it easier for the surgeon to determine inframammary fold and expander/implant placement, more protection between the prosthetic implant and poorly-vascularized mastectomy skin, a larger initial sub-muscular pocket that can result in more efficient use of the native mastectomy flaps, more rapid expansion, and more time to finish the reconstruction [500,501]. Improved
management of threatened implants and a lower incidence of capsular contracture are other benefits revealed by ADM studies [500-503]. Berna and colleagues [504] described a significant benefit of one-stage IBR, reporting “Rapid return to work and prompt administration of adjuvant therapy when needed are further advantages. Moreover, the ADM/mesh-assisted wrapping technique is a muscle sparing-technique that can achieve good cosmetic outcome while preserving the pectoralis major muscle elevation and occurrence rate of other minor complications.” The longer a patient is away from work, the more impact it may have on personal finances, potentially higher insurance bills, and potential stress on the employer. Using ADM for a one-stage IBR can reduce or eliminate these negative outcomes.

2.6.2 Analysis of NSQIP Database in patients undergoing ADM-assisted breast reconstruction: complication rate with ADM

All surgical procedures have associated risks that, although carefully managed and controlled, can result in complications. The reported outcomes for ADM compared with traditional non-ADM techniques vary extensively [505, 506]. A review published by Kim and colleagues [507] found ADM-assisted reconstruction-associated complication rates ranged from 8.6%–19.5%. The pooled published average of 15.4% for ADM-associated complications is greater than the non-ADM pooled average of 14.0% and this difference is statistically significant although a difference of 1% is not expected to be very clinically meaningful. Only one well-designed RCT that examined complication rates was published [508]. This study found equivalent outcomes between ADM and non-ADM breast reconstruction, however the conclusions of this study may have been limited by the use of an older, no longer available ADM size and therefore cost [509]. The ongoing randomized controlled Multi Center Canadian Acellular Dermal Matrix Trial may provide more information about complication rates [510].
Few study results have indicated that the use of acellular dermis–based reconstruction is unsafe, and most studies have found acceptable complication rates and improved aesthetic outcomes [511,512]. There are generally no statistically significant differences between the complication rates associated with ADM-assisted reconstruction [3.2%–48.7%] compared with traditional expander reconstruction [eg. wound infection, hematoma or seroma] [512,513].

A study published by Chun and colleagues [514] evaluated 269 ADM-assisted breast reconstruction surgeries and found that the infection rate was 8.9%, the necrosis rate was 23.4%, the seroma formation rate was 14.1%, and the hematoma formation rate was 2.2%. Compared with complete sub-muscular breast reconstruction, the ADM procedure was associated with greater post-operative seroma formation rates and infection rates. In a study of 153 breast reconstructions, Antony and colleagues [512] found a 23.6% overall complication rate; the seroma formation rate was 7.2%; 2.0% of the patients developed a hematoma; 3.9% developed cellulitis; 4.6% developed flap necrosis and 3.3% developed an infection. Rawlani and colleagues [515] found that after 121 breast reconstruction surgeries, the overall complication rate was 16.5%, while the infection, seroma, and flap necrosis rates were 7.4%, 1.7%, and 6.6%, respectively.

Few studies have compared and stratified differences in outcomes with respect to acellular dermis type, radiation exposure, body mass index, or intraoperative expander volume. Becker and colleagues [516] found an overall complication rate of 4%. Losken and colleagues [513] found one case of native skin necrosis in a study of 31 breasts. Between-process differences in changes in the protein and collagen structure that can occur during processing and sterilization might cause differences in revascularization and recellularization.

Higher complication rates have been associated with the use of bovine ADMs. During a median 3-year follow-up of 41 patients [52 breasts] who received ADM breast construction, the complication rates were 7% for human, 14% for porcine, and 31% for bovine ADMs [517].
Study results suggested that ADMs have better resistance to radiation effects compared with standard tissue expander reconstruction [518,519]. Rawlani and colleagues [515] compared the complication rates for adjunct breast irradiation without the use of irradiation [control group]. They found overall complication rates of 30.7% in the treatment group and 13.7% in the control group. They also compared the use of pre-hydrated ADM and freeze-dried ADM and found that the complication rates and outcomes were similar between the groups [515].

Winocour and colleagues [520] found that the 30-day surgical site infection rate is higher when ADM is used for immediate tissue expander breast reconstruction. The national rate is 4.5% for ADMs and 3.2% for non-ADM products. The rates at their institution were 2.1% after use of ADM and 1.6% after use of non-ADM products [520].

The result of these studies indicated that the use of ADM resulted in higher complication rates, compared with the use of non-ADM products. However, the results of an analysis of a National Surgical Quality Improvement Program data set found that the differences in overall complication rates were not statistically significant [5.3% ADM versus 4.9% non-ADM, p=0.396] [521]. The results of another analysis of the same program’s data set indicated that the rates of wound-associated complications [e.g., infection and seroma formation] after use of ADM for prosthesis-based breast reconstruction were significantly lower than those published in single-institution reports [522].

2.6.3 Tolerance of ADM to chemo-radiation

The use of ADM has been thoroughly discussed and found to result in favorable effects with normal to below normal complication rates in comparison with what was anticipated. However, the treatment outcome needs to be examined further when ADM is subjected to chemotherapy, radiation therapy or both. The following cited studies
examined use of ADM in breast surgery patients who underwent chemo-radiation therapy.

The uncertain association between pre-operative radiation exposure and poor outcomes is likely the result of the negative effects of irradiation on tissue microvasculature, which provokes fibrosis [519,523-526]. Infiltration of fibroblasts into the matrix interferes with incorporation into the surrounding tissue. The probability of successful matrix integration can be negatively affected by serious complications including infection, explantation, seroma, and a poor aesthetic outcome when the ADM stimulates a foreign body response [526-528].

Evidence suggests that exposure to pre-operative radiation is a contraindication for ADM use [529]. However, when ADM is in place before post-operative radiotherapy begins, it can increase the rate of prosthetic pocket expansion and protect against post-operative radiation-induced skin flap necrosis. The pectoralis tightness that can result from post-operative radiation-induced fibrosis may also be lessened when the pectoralis major’s inferior border is released during reconstruction. A study of two-stage prosthetic breast reconstruction [n = 428 breasts] found that explantation rates after post-operative irradiation were reduced in the ADM group compared with previously reported rates [528].

Seth et al. [530] compared an ADM and non-ADM cohort and found that when ADM was not used during reconstruction, there was a 2.63-fold increase in the rate of complications associated with post-mastectomy radiation therapy. No benefits have been found when ADM is used for reconstruction of breasts exposed to pre-operative radiotherapy [465, 523, 531,532].

Many women who undergo breast reconstruction have previous radiation exposure or require post-operative radiotherapy. The literature on whether women who have reconstruction that includes ADM use do better when they also have radiation exposure is contradictory. Some study findings indicate that capsular contracture, infection, revision, and reconstructive failure rates are higher in these women when prothesis-based reconstruction is used [533-535]. Results of analyses of retrospective series that include
pre- or post-operative radiation exposure have been published [465, 536, 537]. Colwell and colleagues [465] found that there were no statistically significant differences in complication rates between radiation groups. Kobraei and colleagues [537] published an analysis of a study population that consisted of a small number of patients found that exposure to post-operative radiation was the only statistically significant variable associated with implant loss in the patients for whom ADM was used as part of their reconstruction.

Results of experimental animal models consistently indicate that ADMs are incorporated and vascularized in fields exposed to radiation or to post-implant radiation [531, 538]. Komorowska-Timek and Gurtner [539] used an animal model to examine radiation effects on implants wrapped in ADM. These implants had decreased inflammation and pseudo-epithelium formation, and matrix incorporation was successful despite radiation exposure [539].

Negative effects can result from delay of chemotherapy to allow more complete incorporation of ADM after IBR [475]. However, use of IBR generally requires no delay or only a modest delay in the start of adjuvant chemotherapy [540, 541]. In some studies, but not all, neoadjuvant and adjuvant chemotherapies have been found to not be associated with increased rates of complications. [542, 543].

2.6.4 Economic disadvantages of ADM

Use of ADM adds several thousand dollars to the costs of breast reconstruction. However, this cost may be balanced by reductions in the numbers of follow-up treatments required when ADM is not used. Results of numerous studies also indicate that these upfront costs are countered by the reduced costs associated with lower complication rates, higher patient satisfaction, and the better QOL experienced by the patient [544-550].
In addition to improvements in outcomes, use of algorithms for decision-making about ADM use may reduce health-care costs because ADM will be used more selectively and, consequently, less frequently. The total cost may be less than use of non-ADM two-stage methods, even when a patient chooses to have additional aesthetic procedures after a direct-to-implant ADM-assisted breast reconstruction [544]. A cost-minimization analysis of the United States health-care setting found that the direct-to-implant reconstruction cost using ADM was US $5,423.02, compared with US $10,934 for use of the traditional non-ADM two-stage procedure [544]. This finding suggests that surgical technique [e.g., direct-to-implant] should be included in decision-making algorithms for ADM use.

Some patients are not candidates for single-stage breast reconstruction. It is difficult to determine whether, compared with the use of similar non-ADM two-stage techniques, ADM use in two-stage techniques is good economic decision. de Blacam and colleagues’ [545] analysis found that the cost of ADM use in two-stage reconstructions was US $11,255 compared with US $10,934 for a similar non-ADM option. The results of Krishnan and colleagues’ [546] analysis was similar, demonstrating that the increase in cost was US $362 when ADM used. This price difference is negligible. However, Bank and colleagues [547] found a US $3,047 greater cost when ADM was used during two-stage reconstruction, which was almost ten times greater compared with Blacam’s or Krishnan’s estimates. Use of ADM alternatives [e.g., dermal allografts] may also result in the same benefits, but at a lower cost [546-549].

The cost-effectiveness of ADM used for two-stage reconstruction can be affected by many variables. The number of post-operative expansion visits can be reduced when it is used for tissue expander surgery because the intra-operative fill volumes are larger compared with similar non-ADM procedures [544,547]. Bank and colleagues [547] suggested that since breast reconstruction costs increase as the numbers of visits for expansion increase, use of ADM for breasts greater than 500 mL volume is cost-effective. From this perspective, including breast size in algorithms may be beneficial, but delayed reconstruction might be necessary for large breasts. The variance in complication rates remains the main reason for the uncertainty about the cost of ADM
use [50,545]. The actual costs are affected by the severities of the associated complication rates, where high severity will increase the overall cost. An algorithm that results in rational selection of ADM use will reduce complication rates and improve the cost-effectiveness of ADM.

Cost of materials is likely the most important factor affecting analyses of ADM cost-utility [546,547]. As such, an algorithm that can help surgeons be more selective choosing patients would substantially improve the practice of cost-effective surgery. A 6 cm × 16 cm ADM sheet is approximately US $3,100. Jordan and colleagues [550] suggested that use of their algorithm could result in a US $150,000 materials costs savings during 1 year of 100 prosthetic breast reconstructions, assuming that the use of the algorithm resulted in a decline in ADM use from 84% to 36% [550].

2.7 Cost-effectiveness analysis (CEA)

Total health-care expenditures in Canada were $182.1 billion in Canadian dollars (CAD) in 2009, CAD $192.9 billion in 2010, and CAD $200.5 billion in 2011 to CAD $242 billion in 2017. These values represented 11.9%, 11.9%, 11.6% and 11.5% of Canada’s gross domestic product in 2009, 2010, 2011 and 2017, respectively [551].

One objective of a health care economic evaluation is to determine the value for money associated with a new intervention. The types of economic evaluations used for CEA include cost-benefit analysis, cost-minimization analysis, and cost-utility analysis [552]. CEA estimates effects on one outcome, which is typically measured using clinical units [e.g., gain in number of symptom-free days or number of life years]. Cost-utility analysis measures patient outcomes in QALYs. A QALY is a unit of measurement of the number of remaining life years multiplied by a QOL factor [weighting factor, 0 [death] to 1 [perfect health]]. Use of QALY as a unified outcome variable facilitates comparison of the cost-effectiveness of different interventions across disease sites and treatments [553].
Cost-effectiveness thresholds vary between countries. Threshold values of US $20,000, US $50,000 or US $100,000 per QALY or life year gained are typically used in individual analyses [554].

2.7.1 Cost-effectiveness of breast cancer treatment

Cost is an important part of the decision-making process for breast cancer treatment. Cost to the government health-care system, the financial burden on the insurance providers, accountability to a private center’s stakeholders and investors, and the direct and indirect financial and non-financial costs to the patients are included in the cost spectrum. The overall costs incurred with a breast cancer patient encompass a broad spectrum of factors such as age of the patient when the disease is first diagnosed, stage of breast cancer, socioeconomic background of the patient, and procedures and device selection. These factors have positive or negative and direct or indirect effects on the cost-effectiveness of breast cancer treatment.

Breast cancer accounts for the greatest numbers of new cancer cases in the United States, with considerable societal resources used to care for these patients [555]. In 2016, greater than 60% of the approximately 250,000 women with a new breast cancer diagnosis [555] were predicted to present with localized, early-stage disease [556]. Evidence-based local management options identified by National Comprehensive Cancer Network Guidelines include mastectomy, mastectomy plus reconstruction, lumpectomy plus whole-breast irradiation, and lumpectomy plus brachytherapy or lumpectomy followed by endocrine therapy alone without radiation [557].

Smith and colleagues [558] found that early-stage breast cancer treatments have different relative values. A treatment with fewer complications may be significantly less expensive than a treatment associated with more complications. However, the treatment decisions made by the patient may be based on factors unrelated to medical value [558]. Smith and
colleagues identified 105,211 women who had early breast cancer that was diagnosed between 2000 and 2011. They examined the data for treatment-related complications within 24 months of the diagnosis and compared complications by type of treatment. A payer's perspective was used for calculation of the mean total and complication-related costs. The results indicated that the most commonly-used treatment was lumpectomy plus whole-breast irradiation and that mastectomy plus reconstruction had almost two times the complication risk of the most commonly-used treatment [54.3% for mastectomy plus reconstruction versus 29.6% for lumpectomy plus whole-breast irradiation among younger women with private insurance; 66.1% for mastectomy plus reconstruction versus 37.6% for lumpectomy plus whole-breast irradiation among older women with Medicare]. Mastectomy plus reconstruction was associated with a higher adjusted total cost [for younger women, a mean value of US $22,481 more; for older women with Medicare, a mean value of US $1,748 more] and higher complication-related cost [for younger women, a mean value US $9,017 greater; for older women, a mean value US $2,092 greater]. Compared with whole-breast irradiation treatment, brachytherapy had slightly greater total costs and complications. Only the women with Medicare insurance had lower lumpectomy-associated costs and complications.

Some of the increase in the use of bilateral mastectomy and reconstruction to treat early breast cancer can be attributed to the recommendation that it is medically necessary, such as in patients with extensive in situ disease or a diagnosis of cancer in high risk or gene mutation carriers. However, nonmedical factors [e.g., patients preferring removal of the entire breast to obtain a more “complete” cancer treatment, those fearing local recurrence when lumpectomy plus whole-breast irradiation is used, or those anxious about the requirement for follow-up visits for mammography screening of the remaining breast] also affect the decision and account for some of the increase.

An important conflict related to “value” in health care is illustrated by the finding that mastectomy plus reconstruction has a significantly higher cost, compared with lumpectomy plus whole-breast irradiation. A higher-cost treatment may be requested by the patient for non-medical reasons even when an equally effective but less expensive treatment is available. Conversations between the patient and her physicians should
include information about the potential for significant complications when mastectomy with reconstruction is used.

2.7.2 Cost-effectiveness of breast cancer screening

It is easy to understand that undergoing mammography can help detect cancer early during the onset of the disease. However, mammography is associated with long-term health effects and costs for scheduled screenings. Mammogram schedules typically vary from annual, biannual, and triennial screening. Various international institutes recommend different frequencies based on their independent conclusions. American recommendations vary from one to two-year intervals while the United Kingdom recommends triennial screening. To improve cost-effectiveness, the recommended age at first screening in the United States is now 50 years of age instead of 40 years of age. In Canada, the recommended screening interval is biennial mammography for average-risk patients, annual mammography for elevated risk patients [first degree relatives, especially those diagnosed at an age younger than 50 years], and annual mammography with annual MRI for high risk patients with greater than 25% lifetime risk of developing breast cancer.

The increasing breast cancer incidence and the accompanying reduced QOL and high medical care costs burden health systems and society. The implementation of national mammography screening programs in many countries [e.g., North America, Europe, Australia, and Japan] has been based on RCT results that indicate that a decline in the breast cancer death rate is associated with mammography screening [559]. However, results of systematic reviews of RCTs of breast cancer screening programs suggested that mammography screening is a less effective intervention than initially believed [560]. CEA can provide the results needed to balance budgets, allocate limited national breast cancer control program resources, and determine the most cost-effective diagnostic and therapeutic care protocols [561].
The parameters used to quantify the cost-effectiveness of a breast cancer intervention include cost to detect a breast cancer, cost to prevent a breast cancer death, and cost per QALY [562]. Cost per year of life expectancy gained is the most relevant parameter for quantification of screening modality cost-effectiveness.

Annual and biennial screening of women 40–49 years of age had a cost per life year gained of US $26,200 and US $14,000, respectively [563,564]. Barratt and colleagues [565] found that beginning screening at 40 years of age instead of 50 years of age would have a per QALY gained cost of US $24,000 to US $65,000. Madan [564] found that the per QALY gained cost for triennial screening of women 47–49 years of age is approximately US $45,000.

Compared with no screening, active screening strategies have a narrow range of incremental cost ratios [i.e., within US $40,000 to US $60,000 of each other]. The incremental ratios increase marginally as screening age eligibility increases from 69 years of age to 74 years of age because the additional screening costs are offset by improved outcomes. Incremental ratios likewise increase when screening age eligibility is reduced from 50 years of age to 40 years of age because the screening costs increase, but there is also a corresponding increase in QALYs gained [566]. The undiscounted overall costs to screen 1,000 average risk women from the general population once each year range from US $11.3 million [50–69 years of age] to US $16.0 million [40–74 years of age] [566]. Screening 1,000 average risk women once every 2 years costs US $8.4 million to US $11.2 million [50–69 years of age and 50–74 years of age, respectively]. Screening 1,000 average risk women once every 3 years costs US $7.6 million to US $8.3 million [50–69 years of age and 50–74 years of age, respectively]. Over a lifetime, the overall cost of no screening for 1,000 women is US $4.9 million [US $4,875 per woman].

An analysis of population-based mammography screening strategies for the Canadian health system used screening diagnostic and treatment cost and utility values. The results indicated that the most cost-effective strategy is biennial screening of women 50–69 years of age and 40–69.27 years of age [467]. That model used different per treatment
costs, did not include triennial screening, and did not include costs associated with lost productivity or negative effects on society [566].

Brown and colleagues’ [568] systematic review found that the range in cost-effectiveness for breast cancer screening was US $3,400 to US $83,830 per life year saved. Other estimates of cost per life year saved range from US $1,634 for a one-time screening at 50 years of age in India [569] to US $45,700 for once per year screening during 50–69 years of age in the United States [570]. A multi-country study of the results of screening every 2 years found that that most cost-effective option was biennial screening from 50–70 years of age [Britain, US $2,685 per life years saved] [571]. The range in cost per QALY gained was US $9,801 [Slovenia, triennial screening 50–65 years of age] to $46,500 [United States, annual screening 50–69 years of age [570]. A 2006 Netherlands study [572] found that the costs per disability-adjusted life year prevented were US $75 for Africa, US $915 for North America, and US $75 for Asia. This study found a considerably lower cost per disability-adjusted life year saved, compared with the other studies [572]. The accuracy and generalizability of the estimated costs and disability-adjusted life years prevented remain to be determined.

A US study of breast cancer screening for women greater than 70 years of age found that compared with no screening, the cost per life year saved was US $35,000 for once per year screening from 80–85 years of age [563]. Barratt and colleagues’ [565] systematic review found that the cost of per QALY gained after changing screening from 50–69 years of age to 50–79 years of age ranged from US $8,119 to US $27,751.

Taken together, the study results indicate that biennial screening from 50–70 years of age is the most cost-effective option for women who are not at high-risk for breast cancer.

The 2016 American Cancer Society guidelines for screening high-risk women for breast cancer recommend that annual MRI and mammography should start at 30 years of age [573]. Because most study results are based on screening younger women at high-risk for breast cancer, there are no data on the effectiveness of screening high-risk patients using MRI and mammography after 69 years of age [574].
The results of RCTs and meta-analyses indicate that mammography screening reduces cancer-associated mortality in the general population. However, there was no evidence that screening reduces mortality in women at high-risk for breast cancer [575]. Prospective studies that began in the 1990s compared MRI with mammography for screening high-risk patients. The results indicated that MRI has significantly greater diagnostic sensitivity, compared with mammography [575-583].

Values for diagnostic sensitivity range from 71%–100% for MRI alone versus 13%–59% for mammography alone. A meta-analysis of 11 studies found that the values for diagnostic sensitivity are 77% for MRI alone, 39% for mammography alone, and 94% for mammography combined with MRI [584]. The higher diagnostic sensitivity of MRI alone is limited by lower diagnostic specificity and increased false-positive rates, which increases the recall rate [for additional imaging] and the biopsy rate [574,575].

Plevritis and colleagues [585] examined the cost-effectiveness of mammography with MRI compared with mammography alone in a population of women at very high-risk for breast cancer [35–54 years of age]. Their results indicated that the costs per QALY were US $55,420 and US $130,695 for BRCA1 and BRCA2 patients, respectively. The estimated costs were US $41,183 [BRCA1 mutation] and $98,454 [BRCA2 mutation] for women with denser breast tissue. Cott and colleagues [586] also examined the cost-effectiveness of MRI combined with mammography for women with BRCA1 and BRCA2 mutations. The results indicated that alternating MRI and digital mammography at 6-month intervals beginning at 30 years of age [i.e., current guideline] is more cost-effective for patients with the BRCA1 mutation than for patients with the BRCA2 mutation [586]. The incremental cost of adding MRI to mammography was US $40,911 per cancer detected [579]. Taneja and colleagues [587] designed a model to evaluate the cost-effectiveness of screening high-risk women using MRI and mammography compared with mammography alone. The incremental cost per QALY for MRI and mammography versus mammography was US $25,270, compared with non-BRCA women [i.e., up to US $315,210]. The results indicated that use of MRI is a cost-effective approach for high-risk patients.
2.7.3 Cost-effectiveness of breast cancer risk reduction techniques

Use of genetic screening for BRCA diagnosis has been possible since the 1990s. The numbers of women who elect to pursue PM based on the results of genetic screening have increased, but only more recently. There are few data on the fiscal effects that the breast cancer treatment options chosen will have on lifetime costs of treatment [588]. Since 2004 and the advent of one-stage IBR, this option has become more popular and mastectomies have also become more popular, particularly the use of BPM [589].

Anderson and colleagues [590] completed a cost-utility analysis comparing different surveillance and preventive strategies in BRCA gene carriers. They estimated that the most cost-effective approach was PM with bilateral salpingo-oophorectomy [BSO]. This approach increased in cost-effectiveness the younger the patient and cost as little as US $100 per QALY gained. However, endometrial cancer, pulmonary emboli, and cataracts were the only complications included in the model. The costs of reconstructive options were not included. The standard threshold used to decide whether a treatment is cost-effective is US $50,000/QALY [i.e., anything below this threshold is considered a worthwhile investment]. Therefore, US $100/QALY is an extremely low cost. Another study found that PM and BSO imparts a survival advantage and results in QALY gains in the highest risk patients [591]. The cost for PM was up to an additional US $1,277/QALY, which is well within the range of cost-effectiveness. A follow-up study [395] found that that BPM and BSO were both less expensive throughout a patient’s lifetime compared with starting with tamoxifen treatment or regular surveillance. In some cases, use of BPM and BSO resulted in more than US $40,000 in savings throughout a patient’s lifetime. Although the study did estimate a contribution to overall patient survival, its estimates suggested there was a slight drop in QOL. A Norwegian study found that there were cost savings when prophylactic BSO and BPM were chosen, especially after including the productivity gains and indirect costs associated with long-term gains, and an increase in life expectancy based on its model of BPM at 30 years of age and BSO at 35 years of age [592].
The results of an analysis of unadjusted and patient preference-weighted data indicated that BPM is more cost-effective than annual mammography when the lifetime breast cancer risk is 50%; the mean values were US $21,042.50 for BPM, compared with US $20,980.44 for screening alone [593]. When the MRI cost was based on Medicare reimbursement rates, for any level of lifetime risk screening using mammography with MRI was always less cost-effective than BPM. The MRI cost would have to be less than US $177.74 to be more cost-effective than BPM, at a lifetime risk of 20% [the American Cancer Society threshold for annual MRI screening]. At a lifetime risk of 43% and a willingness-to-pay threshold of US $50,000 per life year, BPM with breast reconstruction was a cost-effective alternative. It was also cost-effective at a 26% lifetime risk and a willingness-to-pay threshold of US $100,000 per life year. The results of adding preference ratings to the Markov model indicated that BPM with reconstruction was cost-effective when the lifetime risks were 57% and 51% for willingness-to-pay thresholds of US $50,000 and US $100,000 per QALY, respectively. At these thresholds, use of mammography combined with MRI was never cost-effective compared with mammography screening or BPM. Taken together, the results of the study indicated that projected lifetime breast cancer risk must be ≥50% for BPM to result in cost benefits for the number of lives saved [593].

2.7.4 Cost effectiveness of Chemoprevention

The National Surgical Adjuvant Breast and Bowel Project P-1 trial found that tamoxifen prophylaxis reduced invasive breast cancer risk by nearly 50% [429]. After the results were published, the US FDA approved tamoxifen as a chemopreventive agent for women at higher than average risk. However, the elevated risks associated with tamoxifen use include endometrial cancer and thromboembolic events. Although a large proportion of women are eligible for tamoxifen treatment [594], few agree to it because of the risks of these severe side-effects [595,596]. CEA has been used to identify populations of women who would benefit from tamoxifen treatment. To balance the benefits with the potential
harms, these analyses usually target women at an increased 5-year Gail model risk [597]. The study results indicate that although breast cancer incidence is reduced by tamoxifen treatment, extensive use is not cost-effective because of tamoxifen’s cost, side-effects, and sensitivity to QALY assumptions [598-599]. The studies used RR values for side-effects that were taken from the National Surgical Adjuvant Breast and Bowel Project clinical trial results. The researchers also assumed that the reduction in breast cancer risk was limited to the period during active treatment [usually 5 years]. The results of prospective trials with longer follow-up times indicate that the analyses should be repeated using different assumptions [602,603].

2.7.5 Cost-effectiveness of ADM-assisted breast reconstruction

A cost-minimization analysis was used to compare ADM-assisted direct-to-implant one stage reconstruction with the traditional two-stage approach [no ADM] [49]. A decision analysis model and data from a previous systematic review were used to examine probability values for eight outcomes [no complications, seroma, capsular contracture, hematoma, infection, mastectomy flap necrosis, and implant exposure with salvage or loss]. The results of the modeling indicated that the costs of ADM-assisted direct-to-implant reconstruction and the traditional two-stage approach were CAD $10,734 and CAD $11,251, respectively [49].

Cost savings are associated with direct-to-implant reconstruction because, when compared with the two-stage approach, direct-to-implant reconstruction eliminates the second stage of surgery and has lower revision rates. Estimates of revision rates are obtained from short-term follow-up observational studies. More accurate cost estimates would likely result from long-term follow-up studies of the Canadian health care single-payer system.
De Blacam and colleagues [545] used a cost-minimization analysis of a US health-care model to compare tissue expander/implant reconstruction with and without ADM and direct-to-implant reconstruction with ADM. The probability values for five outcome states [no complications, seroma, cellulitis, skin necrosis, and implant removal] were estimated from results of a systematic review. They found that the expected tissue expander/implant reconstruction cost was US $10,934 [604]. tissue expander/implant with ADM was US $11,255 [605], and direct-to-implant reconstruction was US $5,423.02. The ADM cost [US $321, Medicare fee] and hospital and surgical fee differences were three factors that affected the results of the US analysis compared with Jansen and Macadam’s [49,606] analysis of the Canadian system. Differences in costs between health-care systems are apparent from these two studies. In the US study, De Blacam and colleagues [545] used estimates of US $3000 and US $2000 differences in surgical fees between the procedures. In the Canadian study, equivalent hospital fees were estimated for each technique. A CAD $500 difference in surgical fees between the two procedures was estimated by Jansen and Macadam [49,606].

The cost-benefit analysis to examine ADM use for revisional surgery to achieve cosmetic benefits is more complex. A cost savings to the patient might result from the use of ADM at an initial revisionary surgery if fewer additional revision surgeries are required [607, 608]. Of a series of patients who underwent ADM-assisted aesthetic revisionary procedures, 2.6% [2/78] required subsequent surgery during a mean follow-up time of approximately 12 months [607]. Spear and colleagues [608] found that during a 9-month follow-up, 5.8% [3/52] of patients who had ADM used at the initial or first revisional surgery required additional revisional surgery. These rates were lower than the 40.5% secondary revision rate found by the Allergan Core Study during the 7-year follow-up after breast augmentation surgery and an initial revision [608].
2.8 Outcome after prophylactic mastectomy and immediate reconstruction

BPM is an effective risk reduction option in high-risk women. Mastectomy is a traumatic event and patients most likely agonize over post-procedure appearance, and social and sexual interactions. Breast reconstruction is proposed to improve aesthetic outcomes and HRQOL characteristics.

2.8.1 Quality of life

Studies have found that as many as 72% of patients report favorable psychosocial well-being results after BPM. Compared with baseline values, levels of psychological morbidity and anxiety declined by 6 and 18 months, respectively [p<0.05] [609]. Brandberg and colleagues [610] found that compared with baseline values, there were statistically significant declines in anxiety levels by 6 months and 1 year [p<0.05]. Statistically significant declines in levels of distress about cancer have been found at the 6- and 21-month follow-ups [p<0.05] [611]. The results of Stefanek and colleagues’ [612] study indicated that 86% [n=12] of the patients who underwent BPM thought that they would be affected by moderate or greater levels of breast cancer-related worry, but none had clinically significant levels of depression. Geiger and colleagues [613] found that 56% [n=59] of the patients who had a BPM procedure were concerned about breast cancer after the procedure, but the results for the depression scores indicated that 65% [n=69] were not affected by depression. In one population of women [n=26] who underwent BPM and reconstruction, 11.5% had symptoms that suggested anxiety and 3.8% had symptoms that suggested depression, based on Hospital Anxiety and Depression Scale scores. None of the women who only had BPM [n=2] had scores that indicated they were affected by anxiety or depression [614], recognizing that any study with two patients cannot be used to draw any meaningful conclusions.
Hatcher and colleagues [609] found no statistically significant changes at 6 or 18 months that indicated improvements in body image after BPM [609]. The results of Brandberg and colleagues’ [610] study were similar in that here were no statistically significant changes in body image at 6 or 12 months. They found that at 1 year, more than 50% of the women were dissatisfied with their appearance and body and felt self-conscious and less physically attractive. Gopie and colleagues [611] found that there were statistically significant declines in body image by 6 months post-BPM. The results of studies that examine the effects of BPM on sexual well-being vary. Some have found no negative effects, and some have found statistically significant negative effects on sexual well-being. Hatcher and colleagues [609] found no sexual discomfort and high sexual pleasure at 6 and 18 months after BPM, and there were no statistically significant changes compared to baseline values. Gopie and colleagues [611] found that at the 6- and 12-month follow-ups after BPM, there were no statistically significant changes in the high sexual and partner relationship satisfaction that was present at baseline. Brandberg and colleagues [610] reported that compared with baseline, there were statistically significant changes in pleasure by 1-year post-BPM. There were no statistically significant differences in sexual habit or discomfort. At 6- and 12-months post-BPM, more than 50% of women [15%–31%] had positive reactions to intimate situations or questions about feelings of femininity. Study results suggest that after BPM, patients have persistent feelings of discomfort and loss of sensation in their reconstructed breasts [615-617], which may have negative effects on sexual well-being. More than 69% [69%–94%] reported sensitivity to touch and temperature after BPM with reconstruction [615-618]. Brandberg and colleagues [619] reported that at 6 months and 1 year after BPM, 73% of the women had negative breast sensibility [619].

Evaluations of QOL have found higher or similar satisfaction levels in women in non-reconstruction BPM cohorts, compared with women in cohorts that had BPM with reconstruction [612,614,620]. In these studies, the sample sizes of women who had only BPM were generally small [i.e., 11–38 patients], so the results may not be accurate. Compared with women who choose BPM alone, women who choose BPM with post-mastectomy reconstruction may have expectations that are more difficult to meet. Stefanek and colleagues [612] and Gahm and colleagues [616] found that 86% [n=12]
and 92% \([n=22]\), respectively, of women would recommend BPM to other women at a high breast cancer risk. Another study found that 67% \([n=381]\) of a group of women who had BPM responded that they would definitely or probably choose to have the procedure again \([620]\). Spear and colleagues \([621]\) reported that 100% \([n=11]\) of the women in their study population said they would undergo reconstruction again.

2.8.2 Patient satisfaction

Few studies have examined the psychosocial sequelae of RRM. Six months to 30 months after the procedure, Stefanek and colleagues \([612]\) asked 14 women if they were satisfied with their decision to have RRM. The participants were asked about levels of satisfaction with the decision to have RRM, degree of support from family and friends, physical and emotional recovery, and the side-effects of the procedure. In general, the women reported having high levels of satisfaction, except for those who had breast reconstructive surgery. Four of these 11 women were dissatisfied with the procedure because they experienced post-operative complications such as hematoma and implant rupture. Borgen and colleagues \([622]\) found that during a median 14-year follow-up 6% \([21/370]\) of women in a voluntary national PM registry reported that they had regrets about their decision to have RRM. However, the survey results may have been affected by bias because all of the women volunteered to sign up for the PM registry. Except for satisfaction with the decision to have RRM, and other aspects related to the surgery, there are few studies of other psychosocial sequelae of RRM \([609,620]\). Frost and colleagues \([620]\) also examined data from the large population of women in Hartmann and colleagues’ \([32]\) RRM follow-up study. Ninety percent \([523/639]\) completed a questionnaire that asked about emotional status and satisfaction with the decision to have RRM \([\text{median follow-up, } 14.5 \text{ years}]\). Seventy-four percent reported having decreased emotional concern about developing breast cancer. Seventy percent were satisfied or very satisfied with their decision to undergo RRM. Sixty-seven percent responded that they definitely or probably would make the same choice again. Four factors explained 36% of the variance in
satisfaction [satisfaction with appearance, stress levels, implant problems, and the physician's advice to have the operation]. The patients with higher levels of satisfaction with their appearance, lower stress levels, and fewer post-surgery implant problems reported higher satisfaction levels. Some study results suggest that dissatisfaction or regret after BPM is associated with the physician’s initiating the discussion about having the procedure [620,622].

Most women report no changes in or positive change in stress, emotional stability, self-esteem, feelings of femininity, and sexual relationships with breast reconstruction. Hatcher and colleagues’ [609] prospective UK study examined 79 high-risk women who chose RRM and 64 high-risk women who refused RRM. The results indicated that at 6 and 18 months after surgery, the women who underwent RRM had significantly reduced anxiety and psychological morbidity, while the women who refused RRM experienced no changes in anxiety and psychological morbidity. Any changes in sexual functioning were not statistically significantly different in either group. Brandberg and colleagues [619] examined patient satisfaction with outcomes after BPM and found that for more than 70% of the women they studied, there was high correspondence between preoperative expectations of BPM and their perceptions of outcomes at the 6-month and 1-year follow-ups. Overall, 70% of the patients were satisfied with their BPM-associated outcomes. Sahin and colleagues [623] found that 100% [n=21] of the patients they examined were satisfied with their reconstruction-associated outcomes.

2.8.3 Purpose and Hypothesis

The purpose of this study was to evaluate cost of various reconstruction methods to account for reconstruction related complication costs not captured in any other studies and provide a real cost effectiveness estimate for each option among high risk women using current Canadian costing data. The hypothesis of this study is that, based on suggestive evidence that single stage procedures are less costly in previous limited US studies, that one stage implant based reconstruction will be the most cost effective breast reconstruction option for high risk women.
Chapter 3

Material and method

3.1 Model Overview

We developed a decision-analytic model [Figure 3] to estimate the lifetime clinical and economic consequences of different strategies for managing women at high-risk for breast cancer with no history of breast malignancy. The model begins with a decision to use one of the breast cancer risk management strategies available in the current Canadian clinical practice for high-risk women including: (1) Prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction; (2) Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction; (3) Prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction; (4) Prophylactic bilateral mastectomy with immediate autologous breast reconstruction (with or without TE or breast implant); (5) Prophylactic bilateral mastectomy with immediate one-stage non-ADM (no-flap) breast reconstruction; (6) Prophylactic bilateral mastectomy with delayed breast reconstruction; (7) Prophylactic bilateral mastectomy without breast reconstruction; (8) Intense screening and surveillance [Figure 3a].

Each strategy was followed by a Markov model, which is used to project the lifetime health and economic consequences of a hypothetical cohort of high-risk women undergoing each strategy [Figure 3a]. Markov model structure “A” follows strategies that include bilateral prophylactic mastectomy with any type of immediate breast reconstruction [i.e., strategies 1, 2, 3, 4, and 5]. Markov model structure “B” follows the bilateral prophylactic mastectomy with delayed breast reconstruction strategy [strategy 6]. Markov model structure “C” follows the bilateral prophylactic mastectomy without reconstruction strategy [strategy 7]. Markov model structure “D” follows the intensive screening and surveillance strategy [strategy 8]. These Markov models differed from each other in that additional health states were created to account for possible short and long-term complications or delayed breast reconstruction (if applicable) associated with
different breast cancer risk management strategies. We assumed short-term complications as having skin necrosis, infection and hematoma, or autologous necrosis (if applicable) during the first six months following the surgical interventions [450-453]. We assumed long-term complications as having capsular contracture (if applicable), implant removal (if applicable), or revision surgery due to other complications any time during life-time following surgical interventions [450-453]. We assumed complications would require interventions in outpatient clinics and operating rooms or hospitalization and include those that occur at both the donor and recipient sites in the case of autologous breast reconstruction. The Markov models used were distinctively parameterized according to the type of breast cancer risk management strategy.

Markov model structure “A” simulated monthly transitions among the following nine distinct health states: (1) Initial surgical intervention and no postoperative complication; (2) Skin necrosis; (3) Infection and hematoma; (4) Capsular contracture; (5) Autologous necrosis when applicable; (6) Implant removal; (7) Revision surgery due to other complications; (8) Breast cancer; (9) Death (Figure 1b). Markov model structure “B” simulated monthly transitions among the following 12 distinct health states: (1) Initial surgical intervention and no postoperative complication; (2) Delayed two-stage ADM-assisted TE-implant breast reconstruction; (3) Delayed autologous breast reconstruction (with or without TE or breast implant; (4) Delayed one-stage non-ADM breast reconstruction; (5) Skin necrosis; (6) Infection and hematoma; (7) Capsular contracture; (8) Autologous necrosis; (9) Implant removal; (10) Revision surgery due to other complications; (11) Breast cancer; (12) Death [Figure 1c]. Markov model structure “C” simulated monthly transitions among the following five distinct health states: (1) Initial surgical intervention and no postoperative complication; (2) Skin necrosis; (3) Infection and hematoma; (4) Breast cancer; (5) Death [Figure 1d]. Markov model structure “D” simulated monthly transitions among the following three distinct health states: (1) Initial extensive screening and surveillance; (2) Breast cancer; (3) Death [Figure 3f].

High-risk women entering any Markov model start the model upon receiving the intervention (i.e., surgical intervention or extensive screening) and remained in the first health state unless they develop a short or long-term complication (if applicable), have a
delayed reconstruction (if applicable), develop breast cancer, or die. Because development of a complication maybe associated with subsequent complications [630,631], women who developed any complication (if applicable) remain in that complication’s health state unless they develop another complication, breast cancer or die. Women who develop breast cancer remains in that health state unless they die [Figure 3 b, c, d, e and f].

The analysis was conducted from the Canadian health care payer’s perspective. We applied a discount rate of 1.5% per annum to costs, life years (LY) and quality adjusted life years (QALYs) following recommendations by the Canadian Agency for Drugs and Technologies in Health [632]. We used a lifetime horizon and half cycle correction [633]. We used TreeAge Software (Tree-Age Software, Inc.) to produce and evaluate the decision analytic model.
Figure 3: Decision analytic model for women at high risk for breast cancer.

a Breast cancer risk management decision

Prophylactic bilateral mastectomy with immediate one-stage ADM- assisted implant breast reconstruction

Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction

Prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction

Prophylactic bilateral mastectomy with immediate autologous breast reconstruction (with/without TE or breast implant)

Prophylactic bilateral mastectomy with immediate one-stage non-ADM breast reconstruction

Prophylactic bilateral mastectomy with delayed breast reconstruction

Prophylactic mastectomy without breast reconstruction

Intense screening and surveillance

Markov model structure "A"

Markov model structure "A"

Markov model structure "A"

Markov model structure "A"

Markov model structure "A"

Markov model structure "B"

Markov model structure "C"

Markov model structure "D"

b Schematic representation of Markov model structure “A”
c Schematic representation of Markov model structure “B”

- One-stage no-flap breast reconstruction
- Skin Necrosis
- Infection and Hematoma
- Capsular Contracture
- Autologous Necrosis
- Initial surgical intervention and no postoperative complication
- Two-stage ADM-assisted TE-implant breast reconstruction
- Revision surgery
- Death

- Autologous breast reconstruction
- Implant Removal
- Death

d Schematic representation of Markov model structure “C”

- Skin Necrosis
- Infection and Hematoma
- Breast Cancer
- Initial surgical intervention and no postoperative complication
- Death
Decision

Transition

Transition to the death state

Transition to complication states

Abbreviations: ADM= Acellular dermal matrix; TE= Tissue expander.
3.1.1 Data Sources

We used two main sources to parameterize the model: Ontario administrative datasets relevant to cancer health services research held by the Institute for Clinical Evaluative Sciences (ICES) and data from published sources.

3.1.1.1 Health Administrative Data

The primary source of data was Ontario administrative databases, the population-based administrative databases for Canada’s largest province (population 12.5 million). The Ontario Cancer Data Linkage (cd-link) project is a data release mechanism in which Ontario administrative databases relevant to cancer research, are linked, de-identified, and, with the protections of a comprehensive Data Use Agreement (DUA), provided directly to investigators at academic institutions in Ontario. We used the CD-Link project to access the following administrative databases: Registered Persons Database (RPDB), CIHI Discharge Abstract Database and Same Day Surgery (DAD/SDS), Ontario Health Insurance Plan (OHIP), CIHI National Ambulatory Care Reporting System (NACRS), Ontario Cancer Registry (OCR), New Drug Funding Program (NDFP). Data collection and analysis involving these administrative databases were approved by Western University Research Ethics Board.

Brief description of the Ontario administrative databases used in this study

The RPDB database contains demographic information on all individuals eligible for health insurance coverage in Ontario, including an individual’s date of birth, sex, address, date of death (where applicable), and captures changes in eligibility for health insurance coverage. DAD/SDS
contains administrative, clinical and demographic information on hospital discharges and day surgery in all Ontario facilities. The NACRS dataset contains data describing all visits to the emergency room, day procedures, and high cost ambulatory clinics (namely dialysis and oncology) in Ontario. The OHIP database contains all claims made by physicians (and other health care providers) for insured services provided to residents of the province. The OCR is a provincial database that contains the records for all cases of cancer in Ontario. The OCR collects information on cancer staging, patient demographics, diagnostic confirmation methods, clinical characteristics of primary and secondary tumors, and death. The NDFP database contains patient and treatment data on utilization of systemic intravenous oncology drugs for which reimbursement is being sought through the NDFP. It contains the date, agent name, dose, fee for each agent given and patient clinical data including height, weight, body surface area, age, and diagnosis information.

3.1.2 Cohort identification and stratification

We used the DAD/SDS, OHIP and OCR databases to identify our study cohort consisting of women who were identified at high risk for breast cancer during the period from January 1, 2005 to December 31, 2015 in Ontario. We defined these women as having prophylactic bilateral mastectomy or started organized breast cancer screening (defined as having yearly screening mammography and breast magnetic resonance imaging (MRI) [335]) during the study period.
To identify those who had prophylactic bilateral mastectomy, we started by searching the DAD/SDS database for female records containing at least a matching pair of the Canadian Classification of Health Interventions codes for mastectomy (1YM89, 1YM90, 1YM91, or 1YM92) (i.e., indicating bilateral mastectomy) during the study period. We then searched the OHIP database for a matching pair of mastectomy billing codes (R107, R108, or R117) (i.e., indicating bilateral mastectomy) claimed during the same time period of the earliest DAD/SDS record indicating the bilateral mastectomy to optimize the accuracy of the coding of mastectomy for each of these patients. In order to limit this group to those who had prophylactic bilateral mastectomy, we used the DAD/SDS databases to exclude women with history of surgical interventions to the breast and the OCR database to exclude women with history of cancer at two-month following their earliest DAD/SDS record indicating the bilateral mastectomy.

To identify those who had started organized breast cancer screening during the study period [335], we searched the OHIP database for both mammography billing codes (X184, X185, X172, or X178) and breast magnetic resonance imaging (MRI) billing codes (X441, X445, X446, or X447) claimed repeatedly within 11 to 16-month apart during the study period for the same patients and continuously over patients’ follow-up time. This was done since there are no codes specifically designed to identify breast imaging done through the high-risk screening program. In order to limit our identified group to those who received these imaging procedures for screening, we used the DAD/SDS to exclude women with life-time history of surgical interventions to the breast, the OHIP database to exclude women with history of other breast MRIs at their earliest breast MRI during the study period, and the OCR database to exclude women with history of cancer at two-month following their earliest breast MRI during the study period.
To ensure our cohort identification criteria was satisfied, we limited the study cohort to Ontario residents and those with a minimum of two-year survival following either their earliest screening breast MRI or earliest DAD/SDS admission date for prophylactic mastectomy during the study period. We then stratified our study cohort of high-risk women by their type of breast cancer risk management strategy undertaken. To do that, we used the DAD/SDS database to search for the Canadian Classification of Health Intervention (CCI) specific-breast reconstruction codes (e.g., 1YM90LAPMK for immediate one-stage ADM-assisted implant breast reconstruction, 1YM90LATPK for immediate two-stage ADM-assisted TE-implant breast reconstruction, 1YM90LATP for immediate two-stage traditional TE-implant breast reconstruction) and stratify our study cohort to the following eight subgroups representing the eight strategies in our decision model [Table 1]:

(A1) High-risk women who had undergone any type of prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction, representing strategy (1) in the decision model.

(A2) High-risk women who had undergone any type of prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction, representing strategy (2) in the decision model.

(A3) High-risk women who had undergone any type of prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction, representing strategy (3) in the decision model.
(A4) High-risk women who had undergone any type of prophylactic bilateral mastectomy with any type of immediate autologous breast reconstruction (with or without TE or breast implant), representing strategy (4) in the decision model

(A5) High-risk women who had undergone any type of prophylactic bilateral mastectomy with immediate one-stage non-ADM (no-flap) breast reconstruction, representing strategy (5) in the decision model

(A6) High-risk women who had undergone any type of prophylactic bilateral mastectomy with any type of delayed breast reconstruction, representing strategy (6) in the decision model

(A7) High-risk women who had undergone any type of prophylactic bilateral mastectomy without breast reconstruction over their follow-up time, representing strategy (7) in the decision model

(A8) High-risk women who received organized breast cancer screening to manage their high risk for breast cancer and did not receive any prophylactic surgery over their follow-up time, representing strategy (8) in the decision model

3.1.3 Linkage with Ontario administrative databases

We linked our study cohort back with Ontario administrative databases to collect follow-up information between three-year before and up to ten-year after receiving prophylactic bilateral mastectomy or starting organized breast cancer screening. We used this follow-up information to
measure co-morbidity and match the subgroups of cohort of high-risk women on age and comorbidity, estimate transition probabilities for the Markov models, and estimate the direct healthcare cost per unit time for each health state of the Markov models. Details on these steps are provided in the following subsections:

3.1.3.1 Comorbidity index and propensity score matching:

We linked our study cohort with both the DAD/SDS and OHIP databases to determine co-morbidity through diagnoses or procedures that were recorded for each woman included in the cohort during all patient hospital stays and physician claims between three years before and six months after receiving prophylactic mastectomy or starting organized breast screening.

We used co-morbid diagnoses coded using the method developed by Charlson and colleagues, The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes ,it consists of Diabetes mellitus, Liver disease, Malignancy, AIDS, Chronic Kidney Disease, Congestive Heart Failure, Myocardial infarction, Chronic Obstructive Pulmonary Disease, Peripheral vascular disease, Cerebrovascular Accident, Dementia, Hemiplegia, Connective tissue disease and Peptic ulcer disease. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the
score, the more likely the predicted outcome will result in mortality or higher resource use [634-636].

We then used the propensity score matching method to build comparable subgroups of high-risk women undertaken different types of breast cancer risk management in terms of co-morbidity and age (i.e. at time of prophylactic mastectomy or starting organized breast cancer screening) (637,638). We considered women undertaken prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction (subgroup A3) as our reference subgroup. We used logistic regression to create a propensity score (i.e., likelihood) [637,638], for having prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction, using the Charlson co-morbidity score and age regardless of their individual statistical significance. We used the propensity score to match each woman in the reference subgroup (A3) with up to 4 women in each of the other subgroups (A1), (A2), (A4), (A5), (A6), (A7), and (A8). We considered observations that were within a maximum of +/- 0.01 of women’s propensity score in the reference group for matching and chose the closest match without replacement (i.e., caliper matching without replacement) [637,638]. When no matches were found, that woman was be dropped. We assessed whether the propensity score model was adequately specified by comparing the Charlson co-morbidity score and age between the matched subgroups of our cohort of high-risk women to test whether balance was achieved (Table 2).
3.1.3.2 Transition probabilities for the Markov models:

We linked the propensity score–matched subgroups that undergone prophylactic bilateral mastectomy with the OHIP database to determine short and long-term complications associated with prophylactic mastectomy and different breast reconstruction techniques over up to ten-year follow-up. We defined short-term complications as having skin necrosis, infection and hematoma, or autologous necrosis (if applicable) during the first six months following the surgical interventions. We defined long term complications as having capsular contracture (if applicable), implant removal (if applicable), or revision surgery due to other complications any time during life-time following surgical interventions. To do so, we searched the OHIP database for specific billing codes associated with short-term complications (Z080 and R004 for skin necrosis; Z101, Z102, Z140, and Z740 for infection and hematoma; Z226 for autologous necrosis) and long-term complications (Z142 for implant removal; Z182 and Z135 for capsular contracture; R114 for revision surgery due to other complications) that were claimed for each woman included in each of the matched subgroups during the first six months and up to ten-year, respectively, following prophylactic bilateral mastectomy [Table 2]. We used this information to estimate monthly transition probabilities to the complication health states in the Markov model that corresponds with the prophylactic bilateral mastectomy-based risk management strategy that each matched subgroup represents for the decision model [Table 3].

We also linked the propensity score–matched subgroups with the OCR database to determine diagnoses of breast cancer and with the RPDB database to determine mortality after receiving prophylactic bilateral mastectomy or starting organized breast cancer screening (Table 2). We conducted up to ten-year survival analyses using Kaplan-Meier estimates separately among
women who received any prophylactic bilateral mastectomy regardless of their breast reconstruction technique and those who started organized breast cancer screening. We used this information to estimate all monthly transition probabilities to breast cancer and death states in each Markov model following prophylactic bilateral mastectomy-based risk management strategies and in the Markov model following the screening-based risk management strategy, respectively, in the decision model [Table 3].

To extrapolate transition probabilities to life time we assumed the observed average monthly transition probabilities during the observed 10-year follow up in the studied population to be constant over the extrapolated time period. We used baseline age-specific utilities based on representative values for the general Ontario female population in order to account for background morbidity of the average age of our propensity score-matched cohort (∼50 years old) during their lifetime in the decision model [639] [Table 3].
3.1.4 Direct healthcare cost for the Markov models

The direct costs of healthcare services comprised of inpatient and one day procedure stays, visits to the emergency room and ambulatory clinics, physicians and other health care providers’ services and intravenous oncology drugs. The cost of these services and drugs are all publicly funded in Ontario and recorded in the DAD/SDS, NACRS, OHIP and NDFP databases, respectively. The hospital costing data came from ICES in what is called Case Costing Data, which is an average cost of a procedure at an Ontario hospital for any person having that procedure. We linked the propensity score–matched subgroups with these databases to determine individual case-costs of healthcare services from all records of these databases for each woman included in each of the matched subgroups after receiving prophylactic mastectomy or starting organized screening and up to 10-year of follow-up [640].

For services that implement case-mix methodology and where the unit cost is per weighted case (inpatient and one day procedure stays and visits to the emergency room and ambulatory clinics), a case-cost was a product of the resource weight for the specific episode (which reflects intensity of service utilization and acuity of a particular woman) and the appropriate unit costs (a multiplier known as the Cost Per Weighted Case) [640]. For services with a service-specific cost, such as physician services, tests, diagnostic procedures, and intravenous oncology drugs, a case-cost was simply a unit cost (cost per visit, per hour, per service, per dose of given drug) [640].

We estimated the cost of various service categories using a phase-of-care approach [641-644]. Cost of care for patients having initial surgical or screening intervention to manage high risk of breast cancer or having delayed reconstruction following prophylactic bilateral mastectomy were divided into four clinically relevant phases of care: (1) Initial intervention; (2) Continuing care;
(3) Short-term follow-up; (4) Long-term follow-up. The “initial intervention” phase consisted of the first 6-month following the intervention, the “continuing care” phase consisted of the 6 months following the “initial intervention” phase, the “short-term follow-up” phase consisted of the 4 years following the “continuing care” phase, and the “long-term follow-up” phase consisted of the 5 years following the “short-term follow-up” phase. Similarly, cost of cancer care for patients diagnosed with breast cancer was divided into four clinically relevant phases of care: (1) Diagnostic workup and initial cancer care; (2) Continuing cancer care; (3) Short-term follow-up; (4) Long-term follow-up. The “diagnostic workup and initial cancer care” phase consisted of the first 6-month following the diagnosis with breast cancer, the “continuing cancer care” phase consisted of the 6 months following the “diagnostic workup and initial cancer care” phase, the “short-term follow-up” phase consisted of the 4 years following the “continuing cancer care” phase, and the “long-term follow-up” phase consisted of the 5 years following the “short-term follow-up” phase. Within each phase of care and for each cost category, we calculated the cost per day for each patient and the average cost per day separately for each matched subgroup. We then multiplied these average cost-per-day estimates by 30 days to calculate the average monthly cost of each phase of care by matched subgroups and cost categories [Table 4].

We used the average monthly costs of healthcare services collected for each matched subgroup to estimate the cost per unit time in each state of the Markov model that corresponds with the high-risk management strategy that each matched subgroup represents for the decision model (see cohort identification and stratification) [Table 4]. For example, the average monthly costs of healthcare services collected for the matched subgroup (A3) was used to estimate the cost per unit time in each state of Markov model “A” following strategy (3) in the decision mode
3.1.5 Utilities

Quality of life data cannot be obtained from Ontario health administrative databases and thus we used data from published literature [646-649]. QALY was generated by multiplying the utility (0-1) by LY, for example woman lives for 28 years with Prophylactic bilateral mastectomy with one-stage ADM-assisted implant immediate breast reconstruction means she lives with a utility level of 0.703, this woman will have 19.706 QALYs (28 Years of Life x 0.703 Utility Value = 19.706 QALYs). We used baseline age-specific utilities based on representative values for the general Ontario female population in order to account for background morbidity of the average age of women included in our cohort during their lifetime in the decision model [639]. We derived utility decrements associated with prophylactic bilateral mastectomy and different breast reconstruction techniques, short and long complications and breast cancer from a variety of secondary sources. We calculated utilities by subtracting the utility decrements from the respective baseline utility values [Table 5].
3.1.6 Statistical Analysis

Patient characteristics (age, modified Charlson index to reflect comorbidity, year of intervention, type of reconstruction, complications, breast cancer and survival, and length of follow-up) were described using mean (standard deviation) or count (percentage) as appropriate. Furthermore, we examined differences in patient characteristics among patients using Chi-square and t-tests to assess univariate differences. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).
Chapter 4

Results

4.1 Cohort

This study identified 19,755 Ontarian women who were classified at high risk of breast cancer during the period from January 1, 2005 to December 31, 2015 and met our study inclusion criteria. Of those, 1,962 had prophylactic bilateral mastectomy (10%) and 17,793 (90%) started intense breast cancer screening and surveillance (Table 1). Among those women with prophylactic bilateral mastectomy, 69 women (3.5%) had immediate one-stage ADM-assisted implant breast reconstruction, 28 women (1.4%) had immediate two-stage ADM-assisted TE-implant breast reconstruction, 432 women (22%) had immediate two-stage traditional TE-implant breast reconstruction, 163 women (8.3%) had any type of immediate autologous breast reconstruction (with or without TE or breast implant), 219 women (11%) had immediate one-stage non-ADM (no-flap) breast reconstruction, 226 women (11.5%) had any type of delayed breast reconstruction, and 825 women (42%) had bilateral mastectomies without breast reconstruction. Women who were found to have cancers at the time of their mastectomies were excluded from this study.

Prior to matching, women who had prophylactic bilateral mastectomy were significantly younger and had lower estimated comorbidity scores when compared to their counterparts who were women undergoing intense breast cancer screening and surveillance (Table 1).

Using 1 to up to 4 matching on the estimated propensity score, this study matched prophylactic
bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction group of 432 women with a prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction group of 68 women, with a prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction group of 28 women, with a prophylactic bilateral mastectomy with any type of immediate autologous breast reconstruction of 160 women, with a prophylactic bilateral mastectomy with immediate one-stage no-ADM breast reconstruction of 211 women, with a prophylactic bilateral mastectomy with any type of delayed breast reconstruction group of 224 women, with a prophylactic bilateral mastectomy without breast reconstruction group of 618 women, and with an organized breast cancer screening group of 1,696. No women with prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction were dropped due to poor match quality. Table 2 shows the baseline patient characteristics of the matched prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction group as compared to other groups. As a result of matching, differences between the groups in age and co-morbidity score were eliminated (Table 2).

4.1.1 Breast cancer and survival outcomes

Matched women who had prophylactic bilateral mastectomy were less likely to develop breast cancer (p < .0001; Table 2) and had lower mortality (p = < 0.0001; Table 2) compared to their counterparts of matched women who received an intense breast cancer screening and surveillance.
4.2 Base-case scenario

4.2.1 Lifetime cumulative effectiveness and cost of surgical risk reduction strategies versus intense screening and surveillance.

Compared to the intense screening and surveillance strategy, the surgical risk reduction strategies led to increase of 0.785 QALYs and increase cost of $15,848 per person, which resulted in an ICER of $20,188 per QALY gained.

Compared to the intense screening and surveillance strategy, BPM without breast reconstruction led to an increase of 0.508 QALYs per person and decrease in cost of $ 8,220 per person, which was cost saving. In contrast, BPM with one-stage ADM-assisted immediate breast reconstruction and BPM with one-stage non-ADM immediate breast reconstruction led to an increase of 1.157 QALYs and 0.859 QALYs per person respectively, resulting in an increase of $11,128 and $13,282 per person respectively. While BPM with two-stage TE/implant traditional immediate breast reconstruction, BPM with autologous immediate breast reconstruction, BPM with two-stage ADM immediate breast reconstruction and BPM with delayed breast reconstruction each led to an increase of 0.815 QALYs, 0.951 QALYs, 0.516 QALYs, and 0.691 QALYs per person and an increased cost of $21,088, $23,784, $32,526, and $17,351 per person, respectively. This resulted in ICERs of $25,868, $24,988, $63,010 and $25,087 per QALY gained respectively (Table 5, Figure 4).
4.2.2 Lifetime cumulative effectiveness and cost of BPM with immediate two-stage traditional TE-implant breast reconstruction strategy versus other reconstructive strategies.

Compared to BPM with immediate two-stage traditional TE-implant breast reconstruction, BPM with one-stage ADM-assisted implant immediate breast reconstruction and BPM with one-stage non-ADM immediate breast reconstruction led to an increase of 0.342 QALYs and 0.044 QALYs per person respectively and decrease in cost of $9,960 and $7,807 per person respectively, resulting in a cost saving approach. BPM with two-stage ADM reconstruction led to decrease of 0.299 QALY per person and increase cost of $11,438 CAD, BPM with any type of autologous immediate breast reconstruction led to an increase of 0.136 QALY per person and an increased cost of $2,695 CAD per person, resulting in ICER of $19,732 per QALY gained. while BPM with delayed reconstruction led to a decrease of 0.123 QALY per person and reduction in cost of $3,737 CAD per person. Figure 4 illustrates the differences in costs and effects between the eight model strategies using a cost-effectiveness plane where BPM with one stage ADM reconstruction strategy is visually shown to dominate other strategies.

4.3 QALY gain and budget impact analysis at the population level

In Ontario, the average number of women received BPM annually was 173 women, 7 women received BPM with one-stage ADM-assisted breast reconstruction and 166 women received other than types of breast reconstructions per year (Table 2).
Incorporating BPM into standard practice for women at high risk of developing breast cancer in Ontario would result in total annual net gains of 13.5 QALYs with total budget of $ 1.8 million. Since BPM is considered the current standard of care for these women, incorporating BPM with immediate one-stage ADM-assisted implant breast reconstruction in place of all of the other strategies would result in total annual net gain of 20 QALYs and total annual saving of $1.7 million.

Incorporating BPM with two-stage ADM-assisted TE/Implant breast reconstruction, two-stage traditional TE-implant breast reconstruction, BPM with immediate autologous breast reconstruction, or BPM with immediate one-stage non-ADM breast reconstruction into standard practice would result in total annual net gains of 8.9 QALYs, 14 QALYs, 16 QALYs or 14.9 QALYs with the total budget of $2, $2, $2 or $1.8 million respectively. Incorporating BPM without reconstruction or with delayed breast reconstruction into standard practice would result in total annual net gains of 8.7 QALYs or 12 QALYs with the total budget of $ 1.4 or $ 1.9 million respectively.
Table 1 Patient characteristics of 17,793 Ontarian women identified at high risk of breast cancer during the period from January 1, 2005 to December 31, 2015 in Ontario by type of breast cancer risk management strategy undertaken.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction (n=69)</th>
<th>Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction (n=28)</th>
<th>Prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction (n=432)</th>
<th>Prophylactic bilateral mastectomy with any type of immediate autologous breast reconstruction (with or without TE or breast implant) (n=163)</th>
<th>Prophylactic bilateral mastectomy with any type of immediate non-ADM breast reconstruction (n=219)</th>
<th>Prophylactic bilateral mastectomy without breast reconstruction (n= 825)</th>
<th>Organized breast cancer screening (n=17,793)</th>
<th>P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year when identified at high risk – no. of women (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 – 2007</td>
<td>5 (7.24%)</td>
<td>&lt;5</td>
<td>94 (21.75%)</td>
<td>24 (14.72%)</td>
<td>35 (15.98%)</td>
<td>72 (31.85%)</td>
<td>225 (27.27%)</td>
<td>823 (4.62%)</td>
</tr>
<tr>
<td>2008 – 2010</td>
<td>12 (17.39%)</td>
<td>&lt;5</td>
<td>121 (28%)</td>
<td>53 (32.51%)</td>
<td>69 (31.5%)</td>
<td>76 (33.62%)</td>
<td>263 (31.87%)</td>
<td></td>
</tr>
<tr>
<td>2011 – 2013</td>
<td>17 (24.6%)</td>
<td>11 (39.28%)</td>
<td>144 (33.33%)</td>
<td>63 (38.65)</td>
<td>78 (35.61%)</td>
<td>60 (26.54%)</td>
<td>200 (24.24%)</td>
<td></td>
</tr>
<tr>
<td>2014 – 2015</td>
<td>35 (50.72%)</td>
<td>13 (46.42%)</td>
<td>76 (17.59%)</td>
<td>23 (14.11%)</td>
<td>37 (16.89%)</td>
<td>18 (7.96%)</td>
<td>137 (16.6%)</td>
<td></td>
</tr>
<tr>
<td>Age at initial diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 – 29</td>
<td>6 (8.69%)</td>
<td>&lt;5</td>
<td>31 (7.17%)</td>
<td>9 (5.52%)</td>
<td>17 (7.76%)</td>
<td>&lt;5</td>
<td>5 (0.6%)</td>
<td>377 (2.11%)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>14 (20.28%)</td>
<td>7 (25%)</td>
<td>110 (25.46%)</td>
<td>26 (15.95%)</td>
<td>55 (25.11%)</td>
<td>15 (6.63%)</td>
<td>42 (5.09%)</td>
<td></td>
</tr>
<tr>
<td>40 – 49</td>
<td>25 (36.23%)</td>
<td>12 (42.85%)</td>
<td>159 (36.80%)</td>
<td>67 (41.1%)</td>
<td>79 (36.07%)</td>
<td>96 (42.47%)</td>
<td>187 (22.66%)</td>
<td></td>
</tr>
<tr>
<td>50 – 59</td>
<td>17 (24.63%)</td>
<td>5 (17.85%)</td>
<td>102 (23.61%)</td>
<td>49 (30.06%)</td>
<td>54 (24.65%)</td>
<td>76 (33.62%)</td>
<td>295 (35.75%)</td>
<td></td>
</tr>
<tr>
<td>60 – 69</td>
<td>7 (10.14%)</td>
<td>&lt;5</td>
<td>30 (6.9%)</td>
<td>12 (7.36%)</td>
<td>14 (6.39%)</td>
<td>36 (15.92%)</td>
<td>296 (35.87%)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer during follow-up – no. of women (%)</td>
<td>0</td>
<td>1 (3.5%)</td>
<td>14 (3.24%)</td>
<td>10 (6.13%)</td>
<td>8 (3.65%)</td>
<td>24 (10.61%)</td>
<td>79 (9.57%)</td>
<td>2,504 (14.07%)</td>
</tr>
<tr>
<td>Deaths during</td>
<td>0</td>
<td>0</td>
<td>2 (0.46%)</td>
<td>2 (1.22%)</td>
<td>0</td>
<td>2 (0.88%)</td>
<td>18 (2.18%)</td>
<td>243 (1.36%)</td>
</tr>
</tbody>
</table>
### Charlson co-morbidity score

<table>
<thead>
<tr>
<th>Score</th>
<th>Mean (SD, range)</th>
<th>Score &gt; 0 – no. of women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0579 (0.1204; 0 - 1)</td>
<td>3 (4.34%)</td>
</tr>
<tr>
<td>1</td>
<td>0.0357 (0 - 2)</td>
<td>1 (3.57%)</td>
</tr>
<tr>
<td>2</td>
<td>0.0694 (0 - 3)</td>
<td>28 (6.48%)</td>
</tr>
<tr>
<td>3</td>
<td>0.0736 (0 - 2)</td>
<td>11 (6.74%)</td>
</tr>
<tr>
<td>≥4</td>
<td>0.0594 (0 - 7)</td>
<td>12 (5.48%)</td>
</tr>
<tr>
<td></td>
<td>0.1694 (0.5193; 0 - 6)</td>
<td>12 (5.309%)</td>
</tr>
<tr>
<td></td>
<td>0.0796 (0.25; 0 - 2)</td>
<td>107 (12.96%)</td>
</tr>
<tr>
<td></td>
<td>0.1697 (0.5259; 0 - 14)</td>
<td>718 (12.96%)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 Subgroups were compared against each other using Fisher’s exact or chi-square, as appropriate. All statistical tests were two sided and results were considered significant at the 5% critical level. Statistical analysis was performed using SAS, version 9.3 (Cary, NC).

2 Co-morbid diagnoses were considered present if they were found during one year before and 6 months after identification at high risk of breast cancer.

Abbreviations: ADM= Acellular dermal matrix; TE= Tissue expander.
Table 2 Patient characteristics of 3,428 matched women identified at high risk of breast cancer by type of breast cancer risk management strategy undertaken.

| Characteristic                                                                 | Prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction (n=68) | Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction (n=28) | Prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction (n=423) (reference group for propensity score matching) | Prophylactic bilateral mastectomy with any type of immediate autologous breast reconstruction (with or without TE or breast implant) (n=160) | Prophylactic bilateral mastectomy with immediate one-stage non-ADM breast reconstruction (n=211) | Prophylactic bilateral mastectomy with any type of delayed breast reconstruction (n=224) | Prophylactic bilateral mastectomy without breast reconstruction (n=618) | Organized breast cancer screening (n=1,696) | P value^2 |
|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Year when women identified at high risk – no. of women (%)                     | <5                                                                                                     | 88 (21.8%)                                                                                   | 24 (15%)                                                                                           | 32 (15.16%)                                                                                      | 72 (32.14%)                                                                                      | 163 (26.37%)                                                                                     | 82 (4.83%)                                                                                         | 236 (13.91%)                                                                                       | <0.0001                                                                                       |
| 2005 – 2007                                                                   | 5 (7.35%)                                                                                             |                                                                                             |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |
| 2008 – 2010                                                                   | 12 (17.64%)                                                                                           | 119 (28.13%)                                                                                | 53 (33.12%)                                                                                       | 68 (32.22%)                                                                                      | 76 (33.92%)                                                                                      | 205 (33.17%)                                                                                     | 236 (13.91%)                                                                                       | 26 (25.7%)                                                                                         | .07                                                                                             |
| 2011 – 2013                                                                   | 17 (25%)                                                                                              | 142 (33.56%)                                                                                | 61 (38.12%)                                                                                       | 76 (36.01%)                                                                                      | 59 (26.33%)                                                                                      | 140 (22.65%)                                                                                     | 541 (31.89%)                                                                                       | 837 (49.35%)                                                                                       |                                                                                                  |
| 2014 – 2015                                                                   | 34 (50%)                                                                                              | 74 (17.49%)                                                                                 | 22 (13.75%)                                                                                       | 35 (16.58%)                                                                                      | 17 (7.58%)                                                                                      | 110 (17.79%)                                                                                     | 120 (7.07%)                                                                                       | 436 (25.7%)                                                                                       |                                                                                                  |
| Age at initial diagnosis (years)                                               | <5                                                                                                     | 29 (6.85%)                                                                                  | 9 (5.62%)                                                                                         | 16 (7.58%)                                                                                       | <5                                                                                               | 5 (0.8%)                                                                                         | 5 (0.8%)                                                                                         | 120 (7.07%)                                                                                       | 436 (25.7%)                                                                                       | .07                                                                                             |
| 20 – 29                                                                        | 6 (8.82%)                                                                                              |                                                                                             |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |
| 30 – 39                                                                        | 14 (20.58%)                                                                                           | 109 (25.76%)                                                                                | 26 (16.25%)                                                                                       | 54 (25.59%)                                                                                      | 15 (6.69%)                                                                                      | 41 (6.63%)                                                                                       | 436 (25.7%)                                                                                       | 620 (36.55%)                                                                                       |                                                                                                  |
| 40 – 49                                                                        | 25 (36.76%)                                                                                           | 155 (36.64%)                                                                                | 64 (40%)                                                                                          | 75 (35.54%)                                                                                      | 96 (42.85%)                                                                                      | 186 (30.09%)                                                                                     | 620 (36.55%)                                                                                       | 404 (23.82%)                                                                                       |                                                                                                  |
| 50 – 59                                                                        | 17 (25%)                                                                                              | 101 (23.87%)                                                                                | 49 (30.06%)                                                                                       | 52 (24.64%)                                                                                      | 76 (33.92%)                                                                                      | 275 (44.49%)                                                                                     | 404 (23.82%)                                                                                       | 116 (6.83%)                                                                                       |                                                                                                  |
| 60 – 69                                                                        | 6 (8.82%)                                                                                              | 29 (6.85%)                                                                                  | 12 (7.5%)                                                                                         | 14 (6.63%)                                                                                       | 34 (15.17%)                                                                                      | 111 (17.96%)                                                                                     | 116 (6.83%)                                                                                       |                                                                                                  |                                                                                                  |
| Women diagnosed with breast cancer during the entire follow-up time – no. of women (%) | 0                                                                                                       | 13 (3.24%)                                                                                  | 9 (6.13%)                                                                                         | 7 (3.65%)                                                                                         | 24 (10.61%)                                                                                      | 51 (9.57%)                                                                                       | 436 (25.7%)                                                                                       | 289 (17.04%)                                                                                       | <0.0001                                                                                           |
| Deaths during the entire follow-up time – no. of women (%)                     | 0                                                                                                       | 2 (0.47%)                                                                                   | 1 (0.62%)                                                                                         | 0                                                                                                 | 2 (0.88%)                                                                                       | 8 (1.29%)                                                                                         | 436 (25.7%)                                                                                       | 24 (1.41%)                                                                                         | <0.0001                                                                                           |
| Complications associated with                                                  |                                                                                                         |                                                                                             |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |                                                                                                  |
prophylactic mastectomy and different breast reconstruction techniques.

| Short-term complications during the first 6 months of follow-up time – no. of women (%) |  
| Skin necrosis | 2 (2.94%) | 1 (3.57%) | 7 (1.65%) | 7 (4.37%) | 8 (3.79%) | 31 (14.83%) | 5 (0.8%) | NA |
| Infection and hematoma | 2 (2.94%) | 4 (14.28%) | 35 (8.27%) | 14 (8.75%) | 18 (8.5%) | 20 (8.9%) | 56 (9.06%) | NA |
| Autologous necrosis | NA | NA | NA | 3 (1.87%) | 1 (0.47%) | 1 (0.44%) | NA | NA |

| Long-term complications during the entire follow-up time – no. of women (%) |  
| Implant removal | 11 (16.17%) | 9 (32.14%) | 85 (20%) | 24 (15%) | 39 (18.48%) | 36 (16.07%) | NA | NA |
| Capsular contracture | 13 (19.11%) | 10 (35.71%) | 241 (56.97%) | 51 (31.87%) | 64 (30.33%) | 87 (38.83%) | NA | NA |
| Revision surgery due to other complications | 11 (16.17%) | 12 (42.85%) | 155 (36.64%) | 58 (36.25%) | 71 (33.64%) | 84 (37.5%) | NA | NA |

| Follow-up time – mean in months (SD, range) |  
| 16.55 (13.44, 0.06 – 47.13) | 16.22 (13.71, 0.26 – 44.1) | 54.45 (37.42, 0.06 – 136.53) | 53.19 (33.63, 0.8 – 3908) | 1421.87 (1007.86, 29 – 136.56) | 76.44 (34.4, 5.8 – 135.86) | 65.66 (38.14, 0.9 – 135.86) | 35.85 (28.75, 0.33 – 134.7) | <0.0001 |

| Charlson co-morbidity score |  
| 0.0588 (0.1204; 0 – 1) | 0.0686 (0.27; 0 – 3) | 0.075 (0.287; 0 – 2) | 0.061 (0.26; 0 – 1) | 0.053 (0.174; 0 – 1) | 0.084 (0.279; 0 – 3) | 0.068 (0.279; 0 – 3) | .07 |
| Score > 0 – no. of women (%) | 3 (4.41%) | 1 (3.57%) | 27 (6.38%) | 11 (6.87%) | 12 (5.68%) | 7 (4.46%) | 48 (7.76%) | 108 (6.36%) | .08 |
| 0 | 65 | 27 | 396 | 149 | 199 | 217 | 570 | 1,588 |
| 1 | 2 | 1 | 26 | 10 | 11 | 8 | 45 | 104 |
| 2 | 1 | 0 | 0 | 1 | 1 | 2 | 2 | 0 |
| 3 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 4 |
| ≥4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

1 Patients were matched on the estimated propensity score.
2 Subgroups were compared against each other using Fisher’s exact or chi-square, as appropriate. All statistical tests were two sided and results were considered significant at the 5% critical level. Statistical analysis was performed using SAS, version 9.3 (Cary, NC).
3 Co-morbid diagnoses were considered present if they were found during one year before and 6 months after identification at high risk of breast cancer.
Abbreviations: ADM= Acellular dermal matrix; TE= Tissue expander.
Table 3 Base case monthly probabilities and sources.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Base Case value</th>
<th>Duration in the decision model</th>
<th>Distribution used in PSA</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk of breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following any type of bilateral prophylactic mastectomy</td>
<td>0.000478%</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OCR</td>
</tr>
<tr>
<td>While on organized breast cancer screening</td>
<td>0.001877%</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OCR</td>
</tr>
<tr>
<td><strong>Age-specific risk of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 59 years</td>
<td>0.000215%</td>
<td>1st – 9th year in the model</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>60– 69 years</td>
<td>0.00048%</td>
<td>10th – 19th year in the model</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>70 – 79 years</td>
<td>0.001451%</td>
<td>20th – 29th year in the model</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>80– 89 years</td>
<td>0.004521%</td>
<td>30th – 39th year in the model</td>
<td>Beta</td>
<td>Statistics Canada</td>
</tr>
<tr>
<td>90– 99 years</td>
<td>0.015772%</td>
<td>40th – 49th year in the model</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>≥ 100 years</td>
<td>0.039442%</td>
<td>During and following 50th year in the model</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td><strong>Risk of death associated with breast cancer</strong></td>
<td>0.001988%</td>
<td>Lifetime in the breast cancer Markov states</td>
<td>Beta</td>
<td>RPDB</td>
</tr>
<tr>
<td><strong>Risk of complications by type of surgical-based breast cancer risk management strategy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic bilateral mastectomy with immediate one-stage ADM-</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Assisted implant breast reconstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability (%)</th>
<th>Time Period</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.004963%</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.004963%</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.003231%</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.00353%</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.002937%</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability (%)</th>
<th>Time Period</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.006043</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.025365</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.008739</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.008739</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.011056</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prophylactic bilateral mastectomy with immediate two-stage traditional TE-
### Implant Breast Reconstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.002771</td>
<td></td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.014256</td>
<td></td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.005397</td>
<td></td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.008017</td>
<td></td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.004349</td>
<td></td>
</tr>
</tbody>
</table>

### Prophylactic Bilateral Mastectomy with Any Type of Immediate Autologous Breast Reconstruction (with or without TE or breast implant)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.007428</td>
<td></td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.015145</td>
<td></td>
</tr>
<tr>
<td>Autologous necrosis</td>
<td>0.00315</td>
<td></td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.004965</td>
<td></td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.007238</td>
<td></td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.008485</td>
<td></td>
</tr>
</tbody>
</table>
### Prophylactic bilateral mastectomy with immediate one-stage non-ADM breast reconstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability</th>
<th>Time Period</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.006421</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.014751</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Autologous necrosis</td>
<td>0.000791</td>
<td>During the first 6 months in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.006103</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.00599</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.006796</td>
<td>Lifetime in the breast cancer-free Markov states</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
</tbody>
</table>

### Prophylactic bilateral mastectomy with any type of delayed breast reconstruction

#### Before breast reconstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability</th>
<th>Time Period</th>
<th>Beta</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.001351</td>
<td>During the first 6 months in the breast reconstruction-free Markov states and the breast cancer-free Markov state</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.015467</td>
<td>During the first 6 months in the breast reconstruction-free Markov states and the breast cancer-free Markov state</td>
<td>Beta</td>
<td>OHIP</td>
</tr>
</tbody>
</table>

#### Following breast reconstruction
### Delayed immediate two-stage traditional TE-implant breast reconstruction

<table>
<thead>
<tr>
<th>Event</th>
<th>Beta OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.001625</td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.00658</td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.013687</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.015667</td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.00707</td>
</tr>
</tbody>
</table>

During the first 6 months in the breast cancer-free Markov states following breast reconstruction

### Delayed immediate autologous breast reconstruction (with or without TE or breast implant)

<table>
<thead>
<tr>
<th>Event</th>
<th>Beta OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.009816</td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.013883</td>
</tr>
<tr>
<td>Autologous necrosis</td>
<td>0.001925</td>
</tr>
<tr>
<td>Implant removal</td>
<td>0.002841</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.003814</td>
</tr>
<tr>
<td>Revision surgery due to other complications</td>
<td>0.011521</td>
</tr>
</tbody>
</table>

During the first 6 months in the breast cancer-free Markov states following breast reconstruction

### Delayed immediate one-stage non-ADM breast reconstruction

<table>
<thead>
<tr>
<th>Event</th>
<th>Beta OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin necrosis</td>
<td>0.006421</td>
</tr>
<tr>
<td>Infection and hematoma</td>
<td>0.014751</td>
</tr>
<tr>
<td>Autologous necrosis</td>
<td>0.000791</td>
</tr>
</tbody>
</table>

During the first 6 months in the breast cancer-free Markov states following breast reconstruction
### Implant removal
- **Event**: Implant removal
- **Rate**: 0.00602
- **Description**: Lifetime in the breast cancer-free Markov states following breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

### Capsular contracture
- **Event**: Capsular contracture
- **Rate**: 0.007546
- **Description**: Lifetime in the breast cancer-free Markov states following breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

### Revision surgery due to other complications
- **Event**: Revision surgery due to other complications
- **Rate**: 0.00602
- **Description**: Lifetime in the breast cancer-free Markov states following breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

### Prophylactic bilateral mastectomy without breast reconstruction
- **Event**: Skin necrosis
  - **Rate**: 0.001351
  - **Description**: During the first 6 months in the breast cancer-free Markov states
- **Beta**: Beta
- **OHIP**: OHIP

- **Event**: Infection and hematoma
  - **Rate**: 0.01568
  - **Description**: During the first 6 months in the breast cancer-free Markov states
- **Beta**: Beta
- **OHIP**: OHIP

### Types of delayed breast reconstruction following prophylactic bilateral mastectomy
- **Event**: Delayed immediate two-stage traditional TE-implant breast reconstruction
  - **Rate**: 0.01415%
  - **Description**: Lifetime in the breast cancer-free Markov states before any breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

- **Event**: Delayed immediate autologous breast reconstruction (with or without TE or breast implant)
  - **Rate**: 0.01295%
  - **Description**: Lifetime in the breast cancer-free Markov states before any breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

- **Event**: Delayed immediate one-stage non-ADM breast reconstruction
  - **Rate**: 0.00218%
  - **Description**: Lifetime in the breast cancer-free Markov states before any breast reconstruction
- **Beta**: Beta
- **OHIP**: OHIP

**Abbreviations:** PSA = probabilistic sensitivity analysis; CCO= Cancer Care Ontario; RPDB= Registered Persons Database; OHIP= Ontario Health Insurance Plan; ADM= Acellular dermal matrix; TE= Tissue expander.
**Table 4** Base case monthly cost estimates of healthcare services and sources by type of breast cancer risk management strategy and phase of care.

<table>
<thead>
<tr>
<th>Cost estimates (^1), $</th>
<th>Base Case value</th>
<th>Duration</th>
<th>Distribution used in PSA</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylactic bilateral mastectomy with immediate one-stage ADM-assisted implant breast reconstruction (n= 68)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial intervention phase</td>
<td>4,426.8</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>257.4</td>
<td>From the 7(^{th}) month and up to one year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>211.5</td>
<td>From the 2(^{nd}) to the 5(^{th}) year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>160</td>
<td>Lifetime beyond the 5(^{th}) year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td><strong>Prophylactic bilateral mastectomy with immediate two-stage ADM-assisted TE-implant breast reconstruction(n= 28)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial intervention phase</td>
<td>3852.6</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>335.1</td>
<td>From the 7(^{th}) month and up to one year</td>
<td>Log-logistic</td>
<td>DAD/SDS,</td>
</tr>
</tbody>
</table>
following the initial surgical intervention in the model while in any breast cancer-free Markov states

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cost</th>
<th>Description</th>
<th>Model</th>
<th>DAD/SDS, NACRS, and OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term follow-up phase</td>
<td>344.4</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>321.1</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

Prophylactic bilateral mastectomy with immediate two-stage traditional TE-implant breast reconstruction (n= 423)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cost</th>
<th>Description</th>
<th>Model</th>
<th>DAD/SDS, NACRS, and OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>3033.9</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>701.1</td>
<td>From the 7th month and up to one year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>231.6</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>243.2</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

Prophylactic bilateral mastectomy with any type of immediate autologous breast reconstruction (with or without TE or breast implant) (n= 160)
<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration (Years)</th>
<th>Description</th>
<th>Model States</th>
<th>DAD/SDS</th>
<th>NACRS</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>0.5</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>0.5</td>
<td>From the 7th month and up to one year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>0.5</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>0.5</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
</tbody>
</table>

**Prophylactic bilateral mastectomy with immediate one-stage non-ADM breast reconstruction (n= 211)**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration (Years)</th>
<th>Description</th>
<th>Model States</th>
<th>DAD/SDS</th>
<th>NACRS</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>0.5</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>0.5</td>
<td>From the 7th month and up to one year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>0.5</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>0.5</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic</td>
<td>DAD/SDS</td>
<td>NACRS</td>
<td>OHIP</td>
</tr>
</tbody>
</table>
Prophylactic bilateral mastectomy with any type of delayed breast reconstruction (n= 224)

Following prophylactic bilateral mastectomy and before breast reconstruction (n= 224)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration (Years)</th>
<th>Details</th>
<th>Markov States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>1680.6</td>
<td>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free and breast reconstruction-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>287.7</td>
<td>From the 7th month and up to one year following the initial surgical intervention in the model while in any breast cancer-free and breast reconstruction-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>180.9</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free and breast reconstruction-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>162.3</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free and breast reconstruction-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

Following breast reconstruction

Delayed immediate two-stage traditional TE-implant breast reconstruction (n=103)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration (Years)</th>
<th>Details</th>
<th>Markov States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>1659.9</td>
<td>During the first 6 months following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Continuing care phase</td>
<td>726.6</td>
<td>From the 7th month to one year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>220.2</td>
<td>From the 2nd to the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>233.6</td>
<td>Lifetime beyond the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
</tbody>
</table>

**Delayed immediate autologous breast reconstruction (with or without TE or breast implant) (n=87)**

<table>
<thead>
<tr>
<th>Initial intervention phase</th>
<th>2461.5</th>
<th>During the first 6 months following breast reconstruction in the model while in breast cancer-free Markov states</th>
<th>Log-logistic DAD/SDS, NACRS, and OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing care phase</td>
<td>464.7</td>
<td>From the 7th month to one year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>231</td>
<td>From the 2nd to the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>223</td>
<td>Lifetime beyond the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

**Delayed immediate one-stage non-ADM breast reconstruction (n=34)**

<table>
<thead>
<tr>
<th>Initial intervention phase</th>
<th>974.1</th>
<th>During the first 6 months following breast reconstruction in the model while in breast cancer-free Markov states</th>
<th>Log-logistic DAD/SDS, NACRS, and OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing care phase</td>
<td>218.4</td>
<td>From the 7th month to one year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>165.6</td>
<td>From the 2nd to the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Long-term follow-up phase</td>
<td>204</td>
<td>Lifetime beyond the 5th year following breast reconstruction in the model while in breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

**Prophylactic bilateral mastectomy without breast reconstruction (n=618)**

<table>
<thead>
<tr>
<th>Initial intervention phase</th>
<th>1387.8</th>
<th>During the first 6 months following the initial surgical intervention in the model while in any breast cancer-free Markov states</th>
<th>Log-logistic DAD/SDS, NACRS, and OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing care phase</td>
<td>266.7</td>
<td>From the 7th month and up to one year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
<tr>
<td>Short-term follow-up phase</td>
<td>174.9</td>
<td>From the 2nd to the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
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<tr>
<td>Long-term follow-up phase</td>
<td>167.6</td>
<td>Lifetime beyond the 5th year following the initial surgical intervention in the model while in any breast cancer-free Markov states</td>
<td>Log-logistic DAD/SDS, NACRS, and OHIP</td>
</tr>
</tbody>
</table>

**Organized breast cancer screening (n=1,696)**
<table>
<thead>
<tr>
<th>Phase</th>
<th>Cost</th>
<th>Description</th>
<th>Model State</th>
<th>Log-logistic</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial intervention phase</td>
<td>224.1</td>
<td>During the first 6 months following initial screening in the model while in the breast cancer-free Markov state</td>
<td>From the 7&lt;sup&gt;th&lt;/sup&gt; month and up to one year</td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, and OHIP</td>
</tr>
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<td>Continuing care phase</td>
<td>173.7</td>
<td>Following initial screening in the model while in the breast cancer-free Markov state</td>
<td>From the 7&lt;sup&gt;th&lt;/sup&gt; month and up to one year</td>
<td>Log-logistic</td>
<td>NACRS, and OHIP</td>
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<td>Short-term follow-up phase</td>
<td>157.5</td>
<td>From the 2&lt;sup&gt;nd&lt;/sup&gt; to the 5&lt;sup&gt;th&lt;/sup&gt; year following initial screening in the model while in the breast cancer-free Markov state</td>
<td>Lifetime beyond the 5&lt;sup&gt;th&lt;/sup&gt; year following initial screening in the model while in the breast cancer-free Markov state</td>
<td>Log-logistic</td>
<td>NACRS, and OHIP</td>
</tr>
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<td>Long-term follow-up phase</td>
<td>170.4</td>
<td>Lifetime beyond the 5&lt;sup&gt;th&lt;/sup&gt; year following initial screening in the model while in the breast cancer-free Markov state</td>
<td>Lifetime beyond the 5&lt;sup&gt;th&lt;/sup&gt; year following initial screening in the model while in the breast cancer-free Markov state</td>
<td>Log-logistic</td>
<td>NACRS, and OHIP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Breast cancer (n=394)</th>
<th></th>
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<tr>
<td>Diagnostic workup and initial cancer care</td>
<td>4398.6</td>
<td>During the first 6 months in the breast cancer Markov states</td>
<td></td>
<td>Log-logistic</td>
<td>DAD/SDS, NACRS, OHIP and NDFP</td>
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<tr>
<td>Continuing cancer care</td>
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<td>From the 7&lt;sup&gt;th&lt;/sup&gt; month and up to one year in the breast cancer Markov states</td>
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<td>Log-logistic</td>
<td>NACRS, OHIP and NDFP</td>
</tr>
<tr>
<td>Short-term follow-up</td>
<td>963.9</td>
<td>From the 2&lt;sup&gt;nd&lt;/sup&gt; to the 5&lt;sup&gt;th&lt;/sup&gt; year in the breast cancer Markov states</td>
<td></td>
<td>Log-logistic</td>
<td>NACRS, OHIP and NDFP</td>
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<tr>
<td>Long-term follow-up</td>
<td>1,104</td>
<td>Lifetime beyond the 5&lt;sup&gt;th&lt;/sup&gt; year in the breast cancer Markov states</td>
<td></td>
<td>Log-logistic</td>
<td>NACRS, OHIP and NDFP</td>
</tr>
</tbody>
</table>

<sup>1</sup>All costs were inflated to 2018CAD using the bank of Canada inflation calculator [694].

Abbreviations: PSA= probabilistic sensitivity analysis; ADM= Acellular dermal matrix; TE= Tissue expander; DAD/SDS= CIHI Discharge Abstract Database and Same Day Surgery; OHI= Ontario Health Insurance Plan; NACRS= CIHI National Ambulatory Care Reporting System; NDFP= New Drug Funding Program.
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Overall QALYs</th>
<th>Overall cost</th>
<th>Extensive breast cancer screening alone vs. surgical interventions</th>
<th>Traditional two-stage TE-implant immediate breast reconstruction vs. other breast reconstruction techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive breast cancer screening</td>
<td>18.549</td>
<td>$90,231</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Prophylactic bilateral mastectomy without breast reconstruction</td>
<td>19.057</td>
<td>$82,011</td>
<td>+0.508</td>
<td>−8,220</td>
</tr>
<tr>
<td>Prophylactic bilateral mastectomy with two-stage traditional TE-implant immediate breast reconstruction</td>
<td>19.364</td>
<td>$111,319</td>
<td>+0.815</td>
<td>+$21,088 (dominated)</td>
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<td>Prophylactic bilateral mastectomy with one-stage ADM-assisted implant immediate breast reconstruction</td>
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<td>+$11,128 (dominated)</td>
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<td>Prophylactic bilateral mastectomy with two-stage ADM-assisted TE-implant immediate breast reconstruction</td>
<td>19.065</td>
<td>$122,757</td>
<td>+0.516</td>
<td>+$32,526 (dominated)</td>
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<td>Prophylactic bilateral mastectomy with any type of autologous immediate breast reconstruction (with or without TE or breast implant)</td>
<td>19.501</td>
<td>$114,014</td>
<td>+0.951</td>
<td>+$23,784 (dominated)</td>
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<td>Prophylactic bilateral mastectomy with one-stage non-ADM immediate breast reconstruction</td>
<td>19.408</td>
<td>$103,512</td>
<td>+0.859</td>
<td>+$13,282 (dominated)</td>
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<tr>
<td>Prophylactic bilateral mastectomy with delayed breast reconstruction</td>
<td>19.241</td>
<td>$107,582</td>
<td>+0.691</td>
<td>+$17,351 (dominated)</td>
</tr>
</tbody>
</table>

Abbreviations: ADM= Acellular dermal matrix; TE= Tissue expander; ICER= Incremental cost-effectiveness ratio; QALY= quality adjusted life year.
**Figure 4** Differences in costs and effects between model strategies using a cost-effectiveness plane.

- Extensive breast cancer screening
- Prophylactic bilateral mastectomy without breast reconstruction
- Prophylactic bilateral mastectomy with two-stage traditional TE-implant immediate breast reconstruction
- Prophylactic bilateral mastectomy with one-stage ADM-assisted implant immediate breast reconstruction
- Prophylactic bilateral mastectomy with two-stage ADM-assisted TE-implant immediate breast reconstruction
- Prophylactic bilateral mastectomy with any type of autologous immediate breast reconstruction (with or without TE or breast implant)
- Prophylactic bilateral mastectomy with one-stage non-ADM immediate breast reconstruction
- Prophylactic bilateral mastectomy with delayed breast reconstruction

Abbreviations: ADM= Acellular dermal matrix; TE= Tissue expander; ICER= Incremental cost-effectiveness ratio; QALY= quality adjusted life year.
Chapter 5

Discussion and conclusion

5.1 Discussion

A wide array of treatment strategies are available to manage patients at an elevated risk of breast cancer. These strategies include chemoprevention and prophylactic surgery.

Three selective estrogen receptor (ER) modulators (i.e., tamoxifen, raloxifene, and exemestane) have been extensively studied and approved as chemo preventive agents [650-652]. These medications have been developed as preventive agents and as alternatives to surgery to reduce the breast cancer risk in high-risk women. Tamoxifen has an excellent safety profile, prevents breast cancer in mice and rats, and decreases the risk of development of contralateral breast cancer [653-655]. A 5-year course of tamoxifen treatment reduces the relative risk of breast cancer by 30%–50% [650]. The Study of Tamoxifen and Raloxifene (STAR) clinical trial was initiated in postmenopausal women who had a high breast cancer risk. In the STAR trial, 19,747 eligible postmenopausal women were randomly assigned to a 5-year treatment with tamoxifen (20 mg/day) or raloxifene (60 mg/day). The median follow-up time was 81 months. The results indicated that tamoxifen was a better chemo preventive agent, compared with raloxifene. There were no differences between tamoxifen and raloxifene in 5-year survival rates, but the values for the incidence of uterine cancer, and blood clot and cataract formation were significantly lower in the raloxifene group [651]. Results of
studies of most of chemo preventive agents (i.e. tamoxifen, raloxifene) indicate that they can prevent hormone receptor positive breast cancers [651,652]. The lack of any survival benefit in the prevention trials suggests that these agents may prevent hormone receptor positive breast cancers that would have been cured using current treatments, without having any effect on prevention of aggressive, life-threatening breast cancers [652].

One option for the prevention of breast cancer in the high-risk group is prophylactic mastectomy (PM). Retrospective and prospective studies have investigated the utility of this approach. These studies show an 85%–100% breast cancer risk reduction with an up to 14-year median follow-up time. These results include use of Bilateral Prophylactic Mastectomy (BPM) in high-risk women and use of Contralateral PM (CPM) in women previously diagnosed as having breast cancer [656 -659]. Since 1995, the use of PM have substantially increased. This change probably is a result of elevated public awareness and knowledge about hereditary breast cancer and greater availability and variety of procedures for breast reconstruction [660]. Exposure to public health campaigns and to the experiences of high-profile celebrities have also likely contributed to the increased awareness among women [661]. Compared with other mastectomy techniques, total BPM is the most clinically effective; this approach results in an up 90% reduction in the risk of breast cancer development [662,663].

The aesthetic outcome of reconstruction has improved using skin-sparing mastectomy (SSM) techniques [664]. During SSM, the glandular tissues and nipple-areolar complex (NAC) are removed using en-bloc resection. Satisfactory aesthetic outcomes and minimal postmastectomy deformities and scarring result when the breast contour is optimized using the native breast skin envelope. Reconstruction after mastectomy results in
statistically significant improvements in physical measures and quality of life (QOL), compared with mastectomy alone [664].

There has been a trend towards the use of implant-based breast reconstruction techniques [665-669]. The major choice of patients who undergo a breast reconstruction procedure is prosthesis-based reconstruction [669]. However, this approach imposes various challenges such as skin envelope damage and visible contour irregularities due to tension caused by implant malposition [669]. The increased use of Acellular Dermal Matrix (ADM) after mastectomy indicates an important change in breast cancer management [669-671]. Use of ADM improves perfusion, and it prevents implant-associated damage of the skin envelope and skin closure [670]. ADM also helps in the restructuring of the inframammary fold, enhances lateral mammary fold definition, improves the contour of the lower pole, allows for good positioning of the implant, prevents capsular contracture, and reduces the filling duration required for tissue expansion [671]. Nearly one-half of prosthetic breast reconstructions are performed using ADMs [672]. The main disadvantage of ADMs is the high cost associated with its use. In January 2010, a 6-cm x 16-cm thick ADM sheet was US $3,463 [Jansen; economic analysis] [673]. In spite of this higher cost, ADM has been described as a cost-effective technology for use during two-stage, TE-implant immediate breast reconstruction (IBR) because the procedure is more likely to be successful [674]. ADM direct-to-implant reconstruction has a lower cost than two-stage non-ADM reconstruction [673]. In addition to ADMs, de-cellularised tissue derived from other tissue sources, such as the pericardium and peritoneum, have also been developed which have similar properties. With the increasing number of products available on the market, the obvious question becomes whether one product has
advantages over the others. Few studies have been published comparing performance and complications among ADM [516-517]. Given the high cost of ADM, and their different rates of infection, inflammatory reactions, and seroma formation, such a comparison is justified. The widespread acceptance of the technique together with concerns regarding the high cost of ADMs has led to the development of alternative synthetic mesh types for use in breast reconstruction, such as Ti-LOOP Bra, SeriSilk, TIGR® Matrix Surgical Mesh and Vicryl mesh [675-681].

Introduction of new medical technology (e.g., devices, drugs, medical procedures, and policies) often results in significant benefits. However, in the context of limited resource availability, the adoption decision is a challenge that affects every health-care system. Decision makers and society work to maximize the total conferred aggregate health benefit when given specific levels of available resources [682]. In the often-used cost effective analysis (CEA) framework, the “value-for-money” of a newly-developed medical technology can assessed and an adoption decision can be taken. International decision-making bodies (e.g., the National Institutes for Health and Clinical Excellence in the United Kingdom [683], and the Pharmaceutical Benefits Advisory Committee in Australia [684], include CEA in their formal processes used for review of new medical technology and inform health technology adoption decisions [685]. In Canada, the Common Drug Review at the national- and provincial-level committees (e.g., the Ontario Committee to Evaluate Drugs or Cancer Care Ontario) consider CEA results when reimbursement for use of a new pharmaceutical is considered [686]. The primary objective of CEA is to compare the incremental costs and benefits associated with introducing a novel surgical technique or medical technology into an existing standard of
care. Costs are displayed as currency units; benefits are displayed in units related to life expectancy (i.e., “life years gained”). The frequent use of “life years gained” as the cardinal outcome variable in CEA is considerably restrictive. An effective outcome measure for CEA combines the quality and quantity of the outcomes [687]. Therefore, Quality Adjusted Life Years (QALY) has become the most widely used variable in CEA. During the analysis, these life year values are obtained after adjustment by a value from 0 to 1 to reflect differences in QOL variables for different health conditions. CEA results are usually presented as the incremental cost-effectiveness ratio (ICER). The ICER associated with incorporation of a new medical technology is

\[
\text{ICER} = \frac{\text{Cost New} - \text{Cost Current}}{\text{Health New} - \text{Health Current}}
\]

Because CEA involves marginal cost and benefits, the choice of which current standard of care or technology to compare (i.e., the appropriate definition for “Current”) can affect the calculation and the results of a CEA. Therefore, CEA is very sensitive to the choice of strategies being compared. The new medical technology is considered “cost-effective” based on a value of judgment (what cost is considered a good price for an additional outcome) [688]. Heuristics used to assist with making this value judgment include plotting the incremental cost and effectiveness in a cost-effectiveness plane [30],
comparisons with other technologies using a league table [689], and comparisons with pre-specified thresholds (e.g., £30,000/QALY gained in UK [690] or $100,000/QALY gained in Canada) [682,691]. In the first of the two most used approaches for parameterization during CEA of a new medical intervention, the data is estimated directly from a single clinical trial (i.e., use of resources is collected at the same time that the clinical trial is performed). The experimentally-obtained economic data are usually analyzed using the same methods as for the analysis of the clinical data. In the second approach, data from different sources are combined during use of decision-analytic models (e.g., Markov models, decision trees and Monte Carlo simulation models) [692,693]. The data for modeling-based CEA could be a mix of observational data (e.g., resource-use data extracted from reviews of patient charts or from a claims database), experimental (e.g., randomized clinical trial efficacy data), routine statistics (e.g., unit cost or price of resources data), local surveys (e.g., the effects of therapies on QOL variables), or expert opinions (e.g., data that describe the physical quantities of resources consumed by the strategies being compared). Even randomized clinical trial-based CEAs often use data not obtained from a clinical trial (e.g., price or unit cost of a health-care resource). One argument is that a CEA should use experimental data to achieve the greatest internal validity and to comply with biostatistical and epidemiological rules, because the differences between the compared medical interventions are unlikely to be affected by bias [693]. However, the internal and external validity of experimental data, and the CEA results, can be negatively affected by several factors. Typically, only a small proportion of the targeted general population is included in a clinical trial. The experience of the participants enrolled in these trials may not represent
the population-wide experience [694,695]. A measured effect may not be a consequence of exposure to the investigated treatment or technology [696,697]. Relative to the possible durations of effect of the alternatives, clinical trials usually have limited follow-up durations. Use of a “lifetime” horizon is included in many CEA guidelines [698 -701]. This set of factors necessitates extrapolation of clinical trial data when used in CEAs using models (e.g., Markov chain simulation) to assess the long-term effects of the alternative treatment options on cost and effectiveness [698]. Also, randomization may not always be possible, such as in studies that aim to evaluate the effects of drug treatment adherence on real world setting clinical outcomes. Model-based CEA offers the potential for generalization and for application of the results to other settings. However, clinical (experimental and observational) and economic data reported in the literature, and commonly used in these analyses, may not be entirely relevant to the population in the studied geographic region and setting in which alternatives are likely to be used in the real world [699]. Data used for CEA should be extracted from settings that accommodate socioeconomic variability. These data are likely to reflect the relevant patient population’s typical clinical and economic experience in the studied geographic region, during long follow-up periods [700].

Administrative health databases and disease registries are valuable clinical and economic data sources for modeling-based CEAs [701]. These databases include records of events that have occurred under everyday conditions. The main advantage of using these databases is that interventions or technologies studied in CEAs can be described under actual “real world” conditions that are relevant to the studied geographic region [700]. Using Administrative health databases may slightly underestimate the true high-risk
population prevalence because this type of study using administrative data requires women to have sought medical care and have their high risk diagnosed, recorded in electronic medical records and coded in the billing data. The alternative is to use literature from clinical trials or to use observational studies data. These often population-based (i.e., minimizing selection bias) databases have high disease ascertainment (i.e., disease prevalence and incidence) rates. They include large-enough populations that have been studied over time periods long-enough to evaluate effectiveness and costs among different age- or race-specific population subgroups [702,703].

A decision-analytic model was developed to evaluate the cost-effectiveness of BPM with and without different reconstruction techniques to aid in the breast cancer risk reduction decisions for women at high risk of developing breast cancer. The rate of breast cancer is significantly lower (90% relative risk reduction) in patients who undergo risk reducing mastectomy and is accompanied by a survival advantage when compared to the intensive screening and surveillance group [394,395, 656]. However, the significant association between BPM and reduced breast cancer mortality suggests an underlying selection bias for treating potentially healthier women with BPM or aggressive breast cancer biology in surveillance women. As a result, the previously reported associations between BPM and reductions in breast cancer and mortality may partly be attributed to unmeasured factors (i.e., confounders). A randomized prospective trial would be required to minimize the effect of selection bias and determine whether BPM has a real benefit on breast cancer event and mortality. Selecting one type of reconstruction than another is another example of selection bias due to surgeon expertise and women preference. In the base case
analysis, a weighted average of overall costs derived for each strategy from the decision tree is shown in Table 5. When all factors including complications are tallied, BPM without reconstruction is the least expensive risk reducing strategy, followed by BPM with one-stage ADM-assisted implant immediate breast reconstruction and then BPM with one-stage non-ADM immediate breast reconstruction. However, BPM with two stage ADM assisted breast reconstruction was the most expensive with the highest complication rate compared to other strategies. We estimated that BPM with one-stage ADM-assisted implant immediate breast reconstruction and BPM with one-stage non-ADM immediate breast reconstruction have ICERs of $9,615 CAD and $15,457 per QALY gained, respectively. The ICERs of the BPM with immediate one-stage ADM reconstruction strategy was significantly below ICER estimates for the other reconstruction strategies which represents a strategy that has been widely adopted into clinical practice in Canadian jurisdictions. The clinical utility of the different surgical strategies (compared head-to-head) used in our analysis for high-risk women was based on retrospective analyses of the Ontario administrative database obtained from the Canadian Institute for Health Information (CIHI). The ideal study design for evaluating the clinical utility of such surgical intervention and identifying the most cost-effective approach would be a prospective randomized trial in which investigators compare any new procedure with the usual procedure or current practice. Unfortunately, that type of prospective costing data does not exist in the Canadian healthcare system. Additionally, surgical interventions such as modes of breast reconstruction are deeply personal and based on patient body habitus, health comorbidities and cosmetic expectations, and a randomized trial is unethical and impossible to complete. Therefore, our study provides
us with the best possible data to answer this important question of how best to balance resource use with the effectiveness and QALY from each intervention.

In Canada, decisions to permit the use of expensive ADM for reconstruction are being made at the provincial level but the actual per case funding in Ontario for breast reconstruction does not factor or reimburse hospitals for the use of ADM in reconstruction cases regardless of whether it saves a second surgery or not. The processes and criteria used by the provincial ministries of health to evaluate and approve BPM with immediate one-stage ADM reconstruction are still evolving and yet to be defined. National or provincial agencies (e.g., the Canadian Agency for Drugs and Technologies in Health) independently evaluate new technology or product submissions but ADMs are yet to be included. Our results suggest that all of the risk reducing surgical strategies are clinically and economically attractive in high risk women, but that the BPM with one-stage ADM reconstruction may significantly improve the cost-effectiveness and simultaneously provide the most appealing and quickest immediate reconstruction recovery option for these women [Figure 4]. Ultimately, prospective field evaluations (i.e., registry studies) of the BPM with one-stage ADM reconstruction in real world practice for clinically appropriate women may to be the only way to verify the clinical utility of this strategy and identify its cost-effectiveness, however these have not been initiated in any Canadian jurisdictions.

To our knowledge, our study represents the first comprehensive and independent cost-effectiveness analysis comparing the use of available screening to risk reduction using any of the available surgical reconstruction techniques. ADM has received regulatory
approvals through both the United States Food and Drug Administration (FDA) and Health Canada for decentralized testing and its clinical utility is being evaluated in a large Canadian multi-centered randomized clinical trial, the ‘Multi-Center Canadian Acellular dermal matrix Trial (MCCAT) evaluating one-stage implant immediate reconstruction using ADM as compared to the two-stage tissue expander/implant reconstruction but results are not yet available. This study does not include the comparisons to screening (non-surgical) options also available to high risk women, nor would it compare to autologous reconstruction options as in our study. Outcome measures of this ongoing trial do however include aesthetic outcomes, short- and long-term complications, and overall patient satisfaction [510]. ADM use can result in an overall cost savings to the health care system by requiring fewer second stage revision surgical procedures. The cost-effectiveness between different reconstruction techniques remains incompletely understood, however our study showed a clear cost-effective benefit of BPM with immediate one stage ADM-assisted reconstruction with a higher rate of effectiveness compared with women who underwent other risk reducing techniques.

None of the current funding discussions take into consideration the cost to the patient of any of the approaches. For example, when screening with annual MRI and mammogram, the high call-back rate for repeated false positive biopsies accompanied by the significant anxiety and time off work, not to mention the cost to the patient and family if treatment for cancer is required (typically patients require long term disability claims during chemotherapy) are all enormous financial and emotional burdens to patients and their families. Additionally, the cost associated with avoiding a new cancer in a young patient
is not typically considered when weighing the cost of these prophylactic procedures, including the cost associated with a significant proportion of these patients who will become metastatic before ultimately succumbing to the disease. If one stage ADM implant-based reconstruction is adopted as the most cost-effective reconstruction strategy, therefore allowing women the optimal one-stage option with excellent cosmetic outcome, it is likely that more high-risk women will agree to risk reducing surgery and therefore avoid the development of cancer as a result. With the other most common reconstruction options (two-stage tissue expander reconstruction or autologous reconstruction), the cost of prolonged surgical recovery from these breast reconstructions over several months (including several days in hospital for autologous reconstruction and months off work), or the need for weekly hospital visits for tissue expansion followed by a second surgery to replace the expander for the definitive final implant with the two stage tissue expander reconstruction option, can all be prohibitive for single women, young mothers and single income earners. For many of these, a one-stage breast reconstruction allows them the benefit of risk reducing BPM while retaining their psychosexual sense of femininity in a single surgical intervention, which may in fact increase the patient acceptance and compliance with surgical risk reduction as a result.

If we were to use an alternative measure for effectiveness, such as survival, risk reducing surgical techniques would continue to provide a more cost-effective option over intensive imaging surveillance which detects but does not prevent cancer. Patients in the intensive screening program would hopefully have their cancer diagnosed at an earlier stage, although they would likely still require the addition of chemotherapy and the costs and morbidity associated with that, and would be accompanied by the high cost of treating
younger women with breast cancer, many of which who end up developing metastatic disease with the very expensive cost of palliative therapies. Women who elected to undergo BPM with immediate one-stage ADM-assisted reconstruction tended to be younger, however there remains a misconception about the benefits of BPM with one-stage ADM-assisted breast reconstruction, because the ADM itself is expensive. We have shown that, despite the clinical benefit with risk reducing techniques, BPM with immediate one-stage ADM-assisted reconstruction is a more cost-effective option in the management of high-risk women, because it is less costly and provides more effectiveness than a two-stage surgical approach. This cost analysis may assist hospital administrators, physicians and patients alike when deciding whether or not to undergo BPM with immediate breast reconstruction, and it is hoped that hospitals can review this data with the understanding of the impact of permitting ADM use in one-stage reconstruction on the institution’s global budget when both complications and repeat surgeries are considered. These costing arguments do not even factor in the improved quality of life and patient satisfaction associated with one-stage reconstruction and offering patients the very best reconstruction options for them individually (weighing their preferences, comorbidities, body shape and psychosocial goals) should be a top priority for all institutions providing care to Canadian women.

5.2 Strengths and Limitations

The main strength of our study is that the cost measure was derived directly from an Ontario population-wide administration database. This provides a more realistic cost
assessment than the costs derived from other sources. However, our analysis has its limitations. First, the clinical utilities were based on retrospective analyses, thus the outcomes may not necessarily reflect the experience of the high-risk population in Canada or the experience of all women due to potential differences in patient type among the different surgical treatment options (different patient body types may require very different reconstruction decisions). To address this, reports from potential future prospective cohort analyses in real-world Canadian clinical practice can be used to update our model and validate our findings. Second, we assumed relative benefit from surgery to be the same across high risk groups, which was felt to be a reasonable assumption given that there has been no data to date to suggest that some surgical reconstruction strategies preferentially benefit some high-risk women more than others. Third, our study results to different types of ADM (i.e. Human dermis, Porcine dermis, Porcine dermis, Bovine dermis, Bovine pericardium or Porcine peritoneum) with different cost and outcome may add limitation to our study. Fourth, we assumed woman who receive bilateral prophylactic mastectomy or annual bilateral mammogram and MRI are high risk for breast cancer and that due to lack of specific codes for high risk in CCI and OHIP and OBSP. Fifth, limited follow-up time among some of our cohort by differences in time of intervention (some had 10 years and some had 3 years follow-up). Sixth, the hospital costing data is really an average so in some hospitals it will underestimate the true cost and in other hospitals will overestimate the cost so although that is a potential limitation (that it isn’t the true cost of those exact people in the study) it gives us a rough idea. Finally, generalization of our study results to other health care systems may also be limited by differences in hospital management at varying centers (some allowing the use
of ADM and others none, some providing autologous reconstruction and others not), as well as differences in preferences for reconstruction options among the patients themselves, as well as provincial differences in approaches to pricing and reimbursement for the different types of breast reconstruction options.

5.3 Recommendations for future research

There are a number of gaps in our knowledge around bilateral prophylactic mastectomy in research that follow from our findings, and would benefit from further research, including realistic evaluation to extend and further test the theory we have developed here:

1. An In-depth exploration of how one-stage ADM reconstruction could become the most cost-effective strategy and how the different types of ADM materials influence would be very helpful. Further research might compare, for example, economic impact of different ADM materials.

2. More methodological work is needed on how to robustly capture the impact and outcomes of implant versus non-implant strategies in research, including further economic analysis.

3. Research to develop approaches and carry out a full cost–benefit analysis of different reconstructions strategies in high risk women in research would be beneficial. Although methodologically challenging, it would be very useful to conduct some longer-term studies which would seek to quantify the impact of
prophylactic mastectomy on such key indicators as participant recruitment and retention in clinical trials, in order to more accurately follow the clinical outcomes of such patients.

5.4 Conclusions

The choice of breast reconstruction needs to be decided based on the patient body habitus, general condition and patient goals with regards to the cosmetic outcome and the extent of surgery they wish to undergo. BPM with and without reconstruction is likely both clinically and economically attractive, however BPM without immediate breast reconstruction is associated with a lower patient-reported quality of life and has a significant impact on patient sense of self and on their psychosexual well-being. BPM with immediate one-stage ADM-assisted implant breast reconstruction is the most cost-effective strategy and appears to offer the highest value for money. A discussion regarding BPM with immediate one-stage ADM-assisted reconstruction should be individualized to each woman, as this study highlights that the more cost-effective approach depends on each woman’s preference for a particular health state. Every effort should be made by healthcare institutions providing breast care to Canadian women to approve funding for ADM implant-based reconstruction, and all risk reducing strategies should be discussed and the optimal risk reducing strategy offered to all women at high risk of developing breast cancer.
5.5 Acknowledgments

We thank the Department of Epidemiology and Cancer Registry of Cancer Care Ontario and Ontario Health, Healthy Living and Seniors for its support throughout the study. The results and conclusions are those of the authors, and no official endorsement by Ontario Health, Healthy Living and Seniors is intended or should be inferred.
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Appendix A. Ethical Approval

February 17, 2017

Re: Cost-effectiveness of prophylactic mastectomy with different acellular dermal matrix-assisted breast reconstruction techniques for the management of women at high risk for breast cancer

Thank you for submitting the above-referenced study. The HSREB Vice-Chair has reviewed this application and has determined that it does not require review or approval of a Research Ethics Board. In accordance with the Tri-Council Policy Statement 2: Ethical Conduct of Research Involving Humans, Article 2.4, “REB review is not required for research that relies exclusively on secondary use of anonymous information, or anonymous human biological materials, so long as the process of data linkage or recording or dissemination of results does not generate identifiable information.”

In our opinion, the above-referenced research project falls within that description.

We wish you the best of luck with your work.

Most sincerely,
### Curriculum Vitae

<table>
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<tr>
<th>Name</th>
<th>Badria Eid Aljohani</th>
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<tr>
<th>Post-secondary Education and Degrees:</th>
<th>King Abdul-Aziz University, Jeddah, Saudi Arabia 1995-2001 bachelor’s degree in medicine and Surgery (MBBS)</th>
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<tr>
<td></td>
<td>King Fahad general hospital, Medina, Saudi Arabia 2003-2009 Saudi Board in General surgery</td>
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<td>Membership of Royal College of Surgeons (Edinburgh, UK) 2006</td>
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<td>King Faisal specialty hospital &amp; Research Center (KFSH&amp;RC) Riyadh, Saudi Arabia 2012-2013 Breast &amp; Endocrine surgery fellowship</td>
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<td>The university of western Ontario London, Ontario, Canada 2016-2017 Breast ablative and reconstructive fellowship</td>
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<th>Honors and Scholarship Awards:</th>
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<td>3rd Place winner: Abstract in 8th Middle East Best of San Antonio Breast Cancer Symposium; Jeddah, Saudi Arabia 2013/2014</td>
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<td>Breast ablative and reconstructive fellowship 2017</td>
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<th>Related Work Experience</th>
<th>Advanced Trauma Life Support (ATLS) instructor 2005-present</th>
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<td>Assistant Consultant, Breast and Endocrine Surgery unit, Department of Surgery, KFSH&amp;RC, Riyadh, Saudi Arabia Nov 2014-Aug 2015</td>
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<tr>
<td></td>
<td>Al Faisal University Medical School Instructor, KFSH&amp;RC Riyadh, Saudi Arabia Nov 2014-Aug 2015</td>
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