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# **Evaluation of Surveillance Mammography Following Reconstructive Breast Surgery**

G. Philip Barnsley

Thesis submitted to the  
Faculty of Graduate and Postdoctoral Studies  
In partial fulfillment of the requirements  
For the MSc degree in Epidemiology and Community Medicine

Epidemiology and Community Medicine  
Faculty of Medicine  
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## i. Glossary

**Ablative surgeon** General surgeon or surgical oncologist responsible for removal of the breast tumor.

**Breast conserving surgery (BCS)** Removal of only the segment of breast tissue where the cancer is found (lumpectomy). Accompanied by radiation of the affected breast.

### **Breast Reconstruction:**

- **Immediate Breast Reconstruction** Breast reconstruction performed at the time of mastectomy, during the same general anesthetic.
- **Delayed Breast Reconstruction** Breast reconstruction as a second procedure after the mastectomy.
- **Autologous Breast Reconstruction** Breast reconstruction using the patients' own tissue to create the new breast mound. Types of autologous breast reconstruction include:
  - **Free TRAM** Free transverse rectus abdominus flap. A transverse paddle of skin and fat over the lower abdomen is taken with the rectus abdominus muscle and transplanted to the chest to create a new reconstructed breast in the mastectomy site.
  - **Pedicled TRAM** Pedicled transverse rectus abdominus flap. A transverse paddle of skin and fat over the lower abdomen is taken with the rectus abdominus muscle and rotated onto the chest while attached to its blood supply from above to create a new reconstructed breast in the mastectomy site.
  - **Latissimus flap** Skin and fat from the back are taken with the latissimus dorsi muscle and rotated under the arm to create a reconstructed breast, usually in association with a breast implant.
- **Tissue Expander** A silicone elastomer shell which is gradually inflated with a sterile saline solution, stretching the overlying skin until it will accept an implant of the desired size.
- **Breast implant** A breast prosthesis consisting of a silicone gel or sterile saline filled silicone elastomer shell.

|                         |                                                                                                                         |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------|
| <b>Contralateral</b>    | The side other than the affected side.                                                                                  |
| <b>DCIS</b>             | Ductal carcinoma in situ. Cancer cells have not penetrated the duct walls. Highly curative early form of breast cancer. |
| <b>Ipsilateral</b>      | The affected side.                                                                                                      |
| <b>Local recurrence</b> | Return of breast cancer at the original site of the primary breast cancer.                                              |

### **Mammography:**

- **Diagnostic mammography** Mammographic examination to assess an abnormal physical finding.
- **Screening mammography** Mammographic examination aimed at early diagnosis of breast cancer in someone without a suspected breast cancer.
- **Surveillance mammography** Mammographic examination in a patient previously treated for breast cancer without a clinical suspicion of a new primary cancer or recurrence.

### **Mastectomy:**

- **Radical Mastectomy** Removal of the breast, pectoralis major and minor muscles and axillary lymph nodes.
- **Modified Radical Mastectomy** Sparing of the pectoralis major muscle.
- **Skin Sparing Mastectomy** A technique used when the patient is going to undergo immediate breast reconstruction where the ablative surgeon removes the breast and nipple areola complex through a circular incision surrounding the nipple areola complex. This leaves the skin envelope of the breast intact, enabling the reconstruction to incorporate native breast skin.

- **Prophylactic Mastectomy** Mastectomy performed on a patient without breast cancer, but who has decided to undergo the procedure due to a significant risk of developing the disease.

**Metachronous** Occurring at different times.

**Surveillance** Follow up of women with a history of cancer in order to identify recurrent cancer at a lower stage.

**Synchronous** Occurring at the same time.

## **ii – Abstract**

**Objective** - There are currently no recommendations on the use of surveillance mammography for women who have undergone breast reconstruction following mastectomy. The objective of this study is to address the needs of this population of women with regards to the inclusion of ipsilateral surveillance mammography in their regular surveillance.

**Methods** – A multimethod approach including (1) a systematic review, (2) a population based cohort study, and (3) an economic analysis was conducted to evaluate this issue.

**Results** - The systematic review found only case reports and case series' addressing the role of surveillance mammography in women who have undergone breast reconstruction following mastectomy. These studies documented that local recurrence does occur in reconstructed breasts, and that these may be detected by surveillance mammography. In the cohort component of the study, variation in practice was found as 39% of women in the cohort underwent at least one surveillance mammogram of their reconstructed breast. Inference on the effectiveness of surveillance mammography of the reconstructed breast could not be made. The economic analysis found that in order to be cost effective, a reduction in metastatic risk of 3.34% following local recurrence detected by surveillance mammography was required.

**Conclusion** - The findings from this thesis point to two recommendations. First, until stronger evidence becomes available, it is prudent to recommend that women with breast

reconstruction undergo yearly bilateral surveillance mammography. Second, future research is required to review patient outcomes and provide the needed clinical evidence to support this practice.

## 1.0 Chapter 1 – Introduction and Study Objectives

### 1.1 Introduction

Breast cancer is the most prevalent cancer and the second leading cause of cancer related death among Canadian women, excluding skin cancer<sup>1</sup>. Most breast cancers are now diagnosed at an early stage<sup>2,3</sup>. Women with early stage breast cancer are treated surgically with either breast conserving surgery (BCS) or mastectomy. Some women who undergo mastectomy choose to undergo breast reconstruction surgery. Thus there are three subgroups of women who have undergone surgical treatment for breast cancer – BCS patients, mastectomy only patients and mastectomy with breast reconstruction patients.

As breast cancer can recur, breast cancer patients need surveillance after surgical treatment. Guidelines for the follow up of breast cancer patients recommend annual mammograms for BCS patients, aimed at detecting ipsilateral recurrences. Mammograms of a mastectomy site are not recommended as there is no breast mound remaining to be imaged by mammography<sup>4</sup>. For the subgroup of breast cancer patients who have undergone mastectomy with reconstruction, there are no specific guidelines regarding whether or not mammography to detect ipsilateral recurrences should be part of their follow-up<sup>1-9</sup>.

Mammography of the contralateral breast is recommended for all breast cancer patients.

Women who have undergone mastectomy with breast reconstruction are a distinct subgroup of breast cancer patients. BCS patients continue to have a breast after their surgery. Patients who have undergone mastectomy without reconstruction have no breast mound after their surgery. Patients treated with mastectomy and reconstruction have had their breast removed, but the reconstruction has created a breast mound that can be imaged

mammographically. Further, residual breast tissue has been shown to exist in skin flaps used in reconstructive surgery. The presence of a breast mound and the possibility of residual breast tissue suggest that patients treated with mastectomy and reconstruction could be followed with mammography.

Guidelines for use of mammography in the surveillance of breast cancer patients are based on information derived from studies of the effectiveness of the procedure<sup>2, 5, 6</sup>. For patients treated with mastectomy and breast reconstruction studies of the effectiveness of the procedure are lacking; the rate of false positive mammograms and the positive predictive value are unknown, and an economic analysis has not been performed. Hence, there are no guidelines for the use of mammography for patients treated with mastectomy and reconstruction. As these guidelines are absent from the surgical and radiological literature, there are no clear directions for patients and physicians concerned about detection of locally recurrent breast cancer.

### *1.2 Overall Objective*

The overall objective of this thesis is to address whether surveillance mammography of the ipsilateral breast should be part of the regular surveillance of women with breast cancer who have undergone breast reconstruction following mastectomy.

### *1.3 Background and Rationale*

As most breast cancers are now diagnosed at an early stage, over 80% of women with breast cancer will be long-term survivors<sup>2, 3</sup>. The combination of the high incidence of breast cancer among Canadian women and the high proportion of long term survivors makes breast

cancer the most prevalent cancer in women<sup>7, 8</sup>. Reports have stated that in Canada there are 151 000 breast cancer survivors<sup>9</sup>, more than 2 million in the US<sup>10</sup> and that this population continues to increase in number<sup>8</sup>. The age-standardized rate of breast cancer in Canada has risen from 82.2 per 100 000 women in 1973 to 102 per 100 000 women in 1992, remaining relatively stable since<sup>11</sup>.

Women with early stage breast cancer (American Joint Committee on Cancer Stage I or II) are faced with a choice of either BCS or mastectomy. Since Fisher et al published the results of a randomized clinical trial comparing mastectomy and BCS in 1985<sup>12</sup>, the number of women undergoing BCS has increased with a corresponding decrease in the proportion of women with breast cancer undergoing mastectomy<sup>13</sup>. In Ontario, the rate of mastectomy decreased from 58.3 per 100 000 women in 1984/85 to 42.9 per 100 000 women ten years later. Thus, despite the appropriateness of BCS in the treatment of women with early breast cancer, mastectomy remains common<sup>14</sup>.

The risk of local recurrence among women treated with BCS and those treated with mastectomy is similar. Locoregional recurrence following mastectomy without reconstruction has been reported to range between 4.5% to greater than 30%<sup>4, 15, 16</sup> while the risk of local recurrence in remaining breast tissue following BCS and radiotherapy has been reported to be 5% to 15%<sup>17-19</sup>. The risk of recurrence following mastectomy and breast reconstruction is discussed in section 1.3.2.

### *1.3.1 Surveillance Mammography*

Mammography without any symptomatic or diagnostic indications following initial treatment of a primary breast cancer is known as surveillance mammography. This differs from



diagnostic mammography, which is performed upon clinical suspicion of local recurrence or new primary breast cancer. Routine surveillance mammography is recommended to detect ipsilateral recurrence after BCS and to detect metachronous contralateral breast cancers<sup>5, 6</sup>. One study has shown that local recurrences of breast cancer detected by surveillance mammograms are at a lower stage than those detected clinically, which would correspond with better expected outcomes<sup>20</sup>. Guidelines from both the American Society of Clinical Oncology (ASCO) as well as the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer recommend regular bilateral surveillance mammograms for all women with a prior diagnosis of breast cancer treated with BCS, and contralateral surveillance mammography for all women treated with mastectomy<sup>6, 21</sup>. Neither of these guidelines make recommendations for women who have undergone reconstructive breast surgery following mastectomy.

A number of studies have addressed the issue of surveillance mammography following the treatment of breast cancer, and the guidelines are based upon these studies. A retrospective study of 827 patients who underwent mastectomy found that mammographic imaging of the mastectomy site did not increase the detection of locally recurrent breast cancer, and the authors recommend against surveillance mammography of the mastectomy site<sup>4</sup>. Another study, with 411 post-mastectomy patients showed that mammography of the mastectomy site did not detect a single local recurrence<sup>22</sup>. A recently published systematic review of surveillance mammography after the treatment of primary breast cancer, describing the current level of evidence guiding the clinician with regard to its use<sup>5</sup>. This review yielded 15 observational studies, and no randomized controlled trials (RCTs) were identified. In response to this lack of evidence, the authors of the systematic review

performed a large population-based cohort study evaluating the rate of subsequent breast surgery following surveillance mammography<sup>11</sup>. Subsequent breast surgery was used as a surrogate for local recurrence or new primary cancer, and it was found that two-thirds of subsequent breast surgery appear to be precipitated by women's symptoms or clinical findings, rather than by surveillance mammography. These findings were interpreted to suggest that either compliance with surveillance mammography may be lower among women with a higher risk of ipsilateral recurrence or contralateral primary breast cancer, or that the effectiveness of surveillance mammography is decreased among women at higher risk of ipsilateral recurrence or contralateral primary breast cancer.

Despite the lack of strong evidence demonstrating the effectiveness of surveillance mammography of the contralateral breast, and ipsilateral breast in the case of BCS, it is currently recommended by both the ASCO and the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer<sup>6, 21</sup>. These recommendations are based on findings that local recurrence in the breast can be detected earlier by surveillance mammography than by physical examination and is potentially curable by mastectomy<sup>23, 24</sup>.

### *1.3.2 Breast Reconstruction Following Mastectomy*

Breast reconstruction following mastectomy can be performed with or without a breast implant. Autologous breast reconstruction (i.e., without an implant) consists of reconstructing the breast mound with the patient's own tissue. The most common type of autologous reconstruction is the transverse rectus abdominus myocutaneous (TRAM) flap. Other options for autologous reconstruction include the latissimus dorsi flap and

uncommonly the gluteus maximus flap. Implant based reconstruction involves placing a breast prosthesis deep to the pectoralis major muscle to recreate the breast mound.

As noted above, women who have undergone mastectomy and breast reconstruction differ from those who have been treated with mastectomy alone or with BCS. Women who undergo BCS continue to have breast tissue that can be imaged mammographically. Those who have undergone mastectomy have no breast mound that can be imaged mammographically. Patients who have undergone breast reconstruction have had their breast tissue removed, but a breast mound has been created that can be imaged mammographically. A number of studies have looked at the presence of residual breast tissue following mastectomy, specifically skin sparing mastectomy which is commonly used for women wishing to undergo breast reconstruction. In these studies, up to 60% of mastectomy sites have been found to contain residual breast tissue, and this proportion is related to the thickness of the skin flaps left following the mastectomy<sup>25-28</sup>. The presence of a breast mound along with the presence of residual breast tissue makes this group of women unique, in that their mastectomy site along with its residual breast tissue could possibly be followed with surveillance mammography.

The proportion of women who undergo breast reconstruction following mastectomy in the United States is 8.3% to 16% in population-based studies, and this rate is increasing over time<sup>29-32</sup>. Patients treated at any one of the National Cancer Institute (NCI) recognized cancer treatment centres were 40% more likely to undergo reconstruction following mastectomy than those treated at non-NCI centres<sup>31</sup>. NCI centres have been found to have post-mastectomy breast reconstruction rates of up to 45%<sup>33</sup>. In Ontario from 1984 to 1995, the rate of post-mastectomy breast reconstruction was 7.9%<sup>14</sup>.

A number of studies have reported the recurrence rates of women treated with mastectomy and breast reconstruction. With 6 years of follow-up, Kroll found that local recurrence occurred in 7.5% of women who had undergone breast reconstruction following mastectomy<sup>34</sup>. Another study found that in a 10 year study period, patients undergoing mastectomy and immediate breast reconstruction for the treatment of breast cancer have a total risk of local recurrence of 2.3% with a mean time to recurrence of 27 months<sup>35</sup>. Spiegel reported on a mean follow-up duration of 9.8 years that patients with invasive carcinoma, stage II or lower, who were treated with mastectomy and immediate reconstruction had a local recurrence rate of 6.8% over the entire follow up period, while those undergoing the same treatment for ductal carcinoma in situ (DCIS) had no recurrences<sup>36</sup>. The discrepancy between these studies is likely the result of the inclusion of patients with DCIS in the study with the lower rate of recurrence. Taken together, these studies show the rate of local recurrence to be between 2.3% and 7.5% in women with early breast cancer who have undergone mastectomy and breast reconstruction. This recurrence rate is comparable to rates reported following BCS or mastectomy without reconstruction. Despite this relatively common adverse event, there is little agreement on the appropriateness of routine mammographic surveillance for patients with breast reconstruction following mastectomy.

### *1.3.3 Surveillance mammography among women with breast reconstruction following treatment of primary breast cancer*

Mammography of autologous breast reconstructions is different from that of implant based reconstructions in that a breast implant is radiopaque, while autologous reconstructions are radiolucent. Hogge et al. have described the findings of mammography of autologous breast

reconstructions. Normal findings include surgical clips and scars, as well as the vascular pedicle supplying the flap. Abnormal findings include fat necrosis, lipid cysts, calcifications, lymph nodes, epidermal inclusion cysts and recurrence of breast cancer<sup>37</sup>. The mammographic appearance of recurrent carcinoma in autologous reconstruction is similar to that of primary breast cancer<sup>38</sup>, and proponents of surveillance mammography feel that surveillance mammograms of breast cancer patients with autologous tissue reconstruction can detect non-palpable cancer before clinical examination<sup>39, 40</sup>. A retrospective review of a single practitioner's practice of women with implant based breast reconstruction reported three cases of occult local recurrence detected by surveillance mammography in three years of follow-up of a sample of approximately 180 patients. Despite the fact that breast implants are radiopaque, the author of this review believes that due to the placement of the implant in the sub-pectoral plane, the mastectomy plane is elevated off of the chest wall which allows for surveillance mammography<sup>41</sup>. Others feel that diagnostic mammography indicated in patients who present post-operatively with suspicious physical findings is sufficient<sup>42</sup>.

There is concern that scar tissue and foreign bodies, such as breast prostheses, complicate the mammographic image and may lead to a high rate of false positive mammograms, leading to further diagnostic tests in women without recurrence. Because of the scar tissue and foreign bodies expected in reconstructed breasts, it is possible that mammography of reconstructed breasts is more complicated and less accurate than routine screening mammography. Even traditional screening mammography in the general North American population is not without flaws. The rate of positive tests ranges from 5.5% to 15.0%, with a positive predictive value of only 4.4% to 12.2%<sup>43</sup>. A false positive mammogram is not a benign event. In addition to cost and potential morbidity of further

testing indicated by a positive mammogram, significant anxiety is afflicted upon the patient. This anxiety has been found to continue beyond the exclusion of a diagnosis of breast cancer<sup>44</sup>.

With the uncertainty well documented in the surgical and radiological literature, there are no clear directions for patients and physicians concerned about detection of locally recurrent breast cancer in women who have undergone breast reconstruction following mastectomy. With the proportion of women undergoing reconstruction following mastectomy increasing,<sup>29-32</sup> the role of surveillance mammography for this group of women is an important clinical issue.

#### *1.3.4 Description of parent Ontario cohort study*

This thesis uses data from an existing Ontario cohort developed in a parent study entitled “A population-based cohort study of surveillance mammography after treatment of primary breast cancer” by Paszat et al.<sup>11</sup> The parent study examined the rates of use of surveillance mammography and the rates of subsequent breast surgery following surveillance mammography. Data used for the parent study included the Ontario Cancer Registry, the Canadian Institute for Health Information, the Ontario Oncology Patient information Systems, the Radiation Oncology Research Unit at Queen’s University at Kingston, the Ontario Health Insurance Plan and the 1991 Canadian Census. Further details of the cohort are given in section 3.2.2.

### *1.3.5 Specific Objectives*

The objectives of this thesis are:

1. To conduct a systematic review of the literature related to surveillance mammography of women who have undergone breast reconstruction following mastectomy.
2. To use data from an existing Ontario cohort to evaluate the detection of local breast cancer recurrence by surveillance mammography in women who have undergone breast reconstruction following mastectomy.
3. To use data from an existing Ontario cohort to evaluate the rate of false positive and false negative surveillance mammograms in women who have undergone breast reconstruction following mastectomy.
4. To compare the rates of both false positive and false negative surveillance mammograms in women who have undergone breast reconstruction following mastectomy (derived from objective 3) to screening mammograms in the general population (derived from the literature).
5. To perform an economic evaluation of surveillance mammography in women who have undergone breast reconstruction following mastectomy.

### *1.3.6 Hypotheses*

The hypotheses to be tested in this thesis are:

1. Surveillance mammography detects local recurrence in the reconstructed breast earlier than clinical examination and diagnostic mammography in women who have undergone breast reconstruction following mastectomy.

2. False positives are more common in surveillance mammograms than in diagnostic mammograms in women who have undergone breast reconstruction following mastectomy.
3. False negatives are more common in surveillance mammograms than in diagnostic mammograms in women who have undergone breast reconstruction following mastectomy.
4. Surveillance mammography of the reconstructed breast in women who have undergone breast reconstruction following mastectomy is cost effective.

#### *1.3.7 Ethics Approval*

The potential ethical concerns for this thesis relate to privacy and confidentiality. All unique identifiers had been previously removed from the data, and these potential ethical issues were addressed in the parent study for which the dataset was created. There was no direct patient contact. This proposal was approved by the Research Ethics Board of the Ottawa Hospital. In compliance with policy of the Institute for Clinical and Evaluative Sciences cells containing less than five patients in the cohort data must be reported as <5.

#### *1.4 Thesis overview*

In Chapter 1 the background and study objectives were presented. In Chapter 2 a systematic review of the literature addressing surveillance mammography of women following treatment for primary breast cancer both with and without breast reconstruction is presented. Chapter 3 presents the population based cohort of women in Ontario whose treatment for primary breast cancer included breast reconstruction. Chapter 4 presents an economic



analysis of bilateral surveillance mammography of women with breast reconstruction.

Finally, summary and conclusions are presented in Chapter 5.

## **2.0 Chapter 2 – Systematic Review**

### *2.1 Chapter overview*

There are no guidelines specifically addressing the role of surveillance mammography of the ipsilateral breast for women who have undergone mastectomy followed by breast reconstruction, and its role remains controversial. The first objective of this thesis is to conduct a systematic review to identify studies specifically addressing this issue. A systematic review addressing the role of surveillance mammography following treatment for primary breast cancer was originally published in 2002<sup>5</sup>. The systematic review presented in this thesis updates the original review, and identifies all previous articles focusing specifically on women treated with mastectomy and breast reconstruction. The current systematic review identified 4 new articles addressing surveillance mammography following treatment for primary breast cancer published since the original systematic review. These studies confirm previous studies that a large proportion of both ipsilateral recurrences and contralateral breast cancers are detected by routine surveillance mammography alone. Eight articles, consisting of case reports and case series (level III evidence), were identified that address the issue of surveillance mammography of the ipsilateral breast in women with breast reconstruction, demonstrating that certain local recurrences are detected by surveillance mammography alone. The current systematic review demonstrates the paucity of evidence and highlights the need for a well designed study to evaluate the role of surveillance mammography for women with breast reconstruction following mastectomy for breast cancer.

## 2.2 *Methods*

### 2.2.1 *Search Strategy*

Two literature searches using the same search strategy used in the original systematic review (Table I) were conducted. Part 1 of this systematic review (section 2.3.1) is an update of the original systematic review evaluating the role of surveillance mammography following treatment for primary breast cancer. The search in Part 1 was limited to all papers published from 1999 until August 2004, as the original review included papers up to and including 1999.

Part 2 (section 2.3.2) identifies and reviews the literature surrounding the use of surveillance mammography of the ipsilateral breast in women with breast reconstruction. This involved the search of all published literature from January 1980 to August 2004. Although the systematic review would ideally be limited to RCTs, the surgical literature is often lacking in these well-designed prospective studies. Although not scientifically sound, many surgical advances continue to take place based upon experience and anecdote, without confirmation by RCTs. As the number of well-designed studies on surveillance mammography in women with breast reconstruction was expected to be small, case reports and small case series were included. The search strategy for Part 2 was the same as for Part 1, with the additional subject headings “Reconstruction” and “Mammaplasty” (Table II). The databases searched for both parts of this systematic review were Medline, Embase, Cochrane Library and the US National Cancer Institute’s clinical trials database. References of all retrieved articles were also hand searched.

As extensive heterogeneity in follow up, mammography regimen, study design and study quality was expected, no meta-analysis of data from the identified studies was planned.

Instead, this systematic review aimed to provide an understanding of the current state of evidence, or lack of evidence, regarding this clinical situation.

### *2.2.2 Review Process*

Using this strategy, 222 citations in Part 1 and 21 citations in Part 2 were identified for retrieval of the abstract. These citations were then reviewed by 2 independent reviewers (GPB & EG) to identify articles that addressed the practice of routine surveillance mammography and its impact on disease outcomes or detection of recurrences. Articles that appeared to meet this criterion from their titles and abstracts were retrieved for further review. Any disagreements between the reviewers were resolved by discussion until consensus was achieved. Where disagreement still existed following discussion, the full text article was retrieved for further review. Foreign language articles were not translated, and relevant data was extracted from their English abstracts.

Using this strategy, 35 articles were retrieved for Part 1, of which 4 were selected for inclusion based on previously established criteria<sup>5</sup> (Table III). None of the studies were excluded due to an insufficient number of cases under study. Studies which included patients with DCIS were included if they also included patients with Stage I or greater breast cancer. Ten articles were retrieved for Part 2, of which 6 were selected for inclusion. Another 2 studies were found by hand searching references of the 6 identified articles in Part 2, bringing the total to 8. Table IV summarizes the process by which articles identified in the search strategy were ultimately included in the systematic review. The Canadian Task Force on Preventive Health Care system for describing levels of evidence was used to evaluate the strength of each study (Table V)<sup>45</sup>.

Table I – Detailed search strategy for studies on surveillance mammography

| Database                                 | Date Range  | Strategy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ovid:                                    |             | 1. breast neoplasms! OR breast cancer.de. OR breast tumor.de.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Medline Embase                           | 1999 - 2004 | <p>2. neoplasms, second primary.de. OR neoplasm recurrence, local.de. OR second cancer.de. OR (ipsilateral adj1 breast.ti,ab.)</p> <p>3. (second adj1 primary adj1 breast adj1 neoplasm?.ti,ab.) OR (second adj1 primary adj1 breast adj1 tumor?.ti,ab.) OR (ipsilateral adj1 breast adj1 tumor?.ti,ab.) OR (contralateral adj1 breast adj1 primary?.ti,ab.) OR (bilateral adj1 cancer?.ti,ab.)</p> <p>4. 1 AND (2 OR 3)</p> <p>5. mammography!.de. OR mammography.de. OR mammography.ti,ab. OR mammogram?.ti,ab.</p> <p>6. surveillance.ti,ab. OR population surveillance!.de. OR seer program.de. OR mass screening!.de. OR screening.de. OR screening test.de. OR (seer adj1 program.ti,ab.)</p> <p>7. (false negative reactions.de.) OR (false positive reactions.de.) OR (predictive value of tests.de.) OR (sensitivity!.de.) OR (likelihood functions.de.) OR (diagnosis, differential.de.) OR (observer variation.de.) OR (reproducibility of results.de.) OR (reference standards.de.) OR (predictive adj1 value?.ti,ab.) OR (false adj1 positive?.ti,ab.) OR (false adj1 negative?.ti,ab.) OR (sensitivity?.ti,ab.) OR (specificity?.ti,ab.) OR (roc adj1 curve?.ti,ab.) OR (test adj1 operating adj1 result?.ti,ab.)</p> <p>8. cohort studies!.de. OR prognosis.de. OR morbidity!.de. OR mortality!.de. OR survival analysis!.de. OR disease progression.de. OR time factors.de. OR risk factors.de. OR cohort analysis.de. OR disease course.de. OR disease severity.de. OR prediction and forecasting.de. OR mortality.de. OR survival.de. OR age factors.de. OR risk.ti,ab. OR (relative adj1 risk.ti,ab.) OR cohort?.ti,ab. OR prognosis?.ti,ab. OR (inception adj1 cohort.ti,ab.) OR (prognostic adj1 factor.ti,ab.) OR course.ti,ab. OR (clinical adj1 course.ti,ab.) OR predict?.ti,ab. OR outcome?.ti,ab.</p> <p>9. clinical trials!.de. OR random allocation.de. OR double-blind method.de. OR risk factors.de. OR practice guidelines.de. OR treatment outcome.de. OR clinical trial.de. OR evidence based medicine.de. OR practice guideline.de. OR grateful med.de. OR medlars!.de. OR multicenter studies.de. OR dt=clinical trial OR dt=clinical trial! OR dt=randomized controlled trial OR sample size.de. OR dt=controlled clinical trial OR dt=multicenter study OR dt=meta-analysis OR dt=review OR dt=short survey OR dt=practice guideline! OR random?.ti,ab. OR (double adj1 blind?.ti,ab.) OR (double adj1 dummy.ti,ab.) OR mask?.ti,ab. OR sham?.ti,ab. OR placebo?.ti,ab. OR (controlled adj1 trial?.ti,ab.) OR efficacy.ti,ab. OR effectiveness.ti,ab. OR metanaly?.ti,ab. OR dersimonian.ti,ab. OR (der adj1 simonian.ti,ab.) OR der?simonian.ti,ab. OR (fixed adj1 effect?.ti,ab.) OR (methodologic adj1 review?.ti,ab.) OR (methodologic adj1 overview?.ti,ab.) OR (collaborative adj1 review?.ti,ab.) OR (integrative adj1 research adj1 review?.ti,ab.) OR (systematic adj1 overview?.ti,ab.) OR (systematic adj1 review?.ti,ab.) OR handsearch?.ti,ab. OR (manual adj1 search?.ti,ab.) OR (pooled adj1 data.ti,ab.) OR (mantel adj1 haenszel.ti,ab.) OR peto.ti,ab. OR (electronic adj1 database?.ti,ab.) OR (bibliographic adj1 database?.ti,ab.) OR medline.ti,ab. OR cinahl.ti,ab. OR psycinfo.ti,ab. OR OR psycinfo.ti,ab. OR psychlit.ti,ab. OR psyclit.ti,ab. OR embase.ti,ab. OR (excerpta adj1 medica.ti,ab.) OR medlars.ti,ab. OR scisearch.ti,ab. OR (science adj1 citation adj1 index.ti,ab.) OR (isi adj1 citation.ti,ab.) OR (web adj1 science.ti,ab.) OR ovid.ti,ab. OR winspirs.ti,ab. OR blaise.ti,ab. OR healthstar.ti,ab. OR cancerlit.ti,ab. OR pascal.ti,ab.</p> <p>10. economics!.de. OR economics.de. OR cost benefit analysis.de. OR economic evaluation.de. OR cost control.de. OR cost effectiveness analysis.de.</p> <p>11. (4 AND 5 AND 6) OR (4 AND 5 AND 7) OR (4 AND 5 AND 8) OR (4 AND 5 AND 9) OR (4 AND 5 AND 10)</p> <p>12. limit 11 to yr=1999 - 2004</p> <p>13. remove duplicates from 12</p> |
| Cochrane Library                         | 1999 - 2004 | 1. Breast neoplasms.de. AND mammography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| NCI CancerNet Search for Clinical Trials | 1999-2004   | 1. Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Table II – Detailed search strategy for identifying studies on mammography following breast reconstruction

| Database | Date Range  | Strategy                                                                                                                                                                                                      |
|----------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ovid:    |             |                                                                                                                                                                                                               |
| Medline  |             |                                                                                                                                                                                                               |
| Embase   | 1980 - 2004 | As with Part I, with the following additions:<br>12. limit 11 to yr=1980 - 2004<br>13. remove duplicates from 12<br>14. Reconstruction! OR Mammoplasty! OR (breast adj1 reconstruction.ti,ab)<br>15. 14 AND 1 |

Table III – Criteria for data extraction for studies on surveillance mammography

| Category                                         | Inclusion Criteria                                       |
|--------------------------------------------------|----------------------------------------------------------|
| Year of Publication                              | 2000 - present                                           |
| Language of publication                          | None (abstraction from abstracts in non-English papers ) |
| Study period                                     | No restrictions                                          |
| Number of cases under study                      | ≥ 100 patients                                           |
| Age at primary diagnosis                         | No restrictions                                          |
| Primary diagnosis (stage)                        | Exclusion of DCIS as primary diagnosis                   |
| Primary treatment                                | No restrictions                                          |
| Rate of recurrence                               | No restrictions                                          |
| Time to recurrence                               | No restrictions                                          |
| Study protocol for mammography surveillance      | No restrictions                                          |
| Rate of detection of recurrence by mammography   | No restrictions                                          |
| Rate of detection of recurrence by other methods | No restrictions                                          |
| Total meeting criteria                           | 4 of 35                                                  |

Table IV – Process for inclusion of articles identified to be related to Part 1 or Part 2

|                                               | <b>Part 1:<br/>Surveillance<br/>mammography</b> | <b>Part 2:<br/>Surveillance mammography<br/>following breast reconstruction</b> |
|-----------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|
| References identified by search strategy      | 222                                             | 21                                                                              |
| Full references retrieved for review          | 35                                              | 10                                                                              |
| References meeting inclusion criteria         | 4                                               | 6                                                                               |
| Additional references found by hand searching | 0                                               | 2                                                                               |
| <b>Total</b>                                  | <b>4</b>                                        | <b>8</b>                                                                        |

Table V – Levels of Evidence<sup>45</sup>

| <b>Level</b> | <b>Description</b>                                                                                                                                      |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| I            | Evidence from randomized controlled trial(s)                                                                                                            |
| II-1         | Evidence from controlled trial(s) without randomization                                                                                                 |
| II-2         | Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group                                           |
| II-3         | Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here |
| III          | Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees                                    |

## 2.3 Results

### 2.3.1 Part 1: Surveillance mammography following treatment of primary breast cancer

Primary data abstracted from each study are presented in Table VI. Only four studies addressed the issue of surveillance mammography after primary breast cancer since the original systematic review was conducted<sup>11, 20, 46, 47</sup>. All of these reported on ipsilateral breast cancer recurrence, and Ashkanani<sup>47</sup> and Paszat<sup>11</sup> also reported on the detection of contralateral breast cancer. Three of these studies were retrospective case series and ranked as level III evidence<sup>45</sup>, and one was a population-based cohort study ranking as level II-2 evidence<sup>11</sup>. The mammography regimen was different in each study, ranging from annual bilateral mammograms to no set protocol.

One of the case series reported ipsilateral recurrences detected by mammography alone only for the first year of follow up<sup>20</sup>. In the two case series that reported beyond one year of follow up, ipsilateral recurrence was detected by mammography alone in 28% and 48% of cases<sup>46, 47</sup>. In the remaining study, two of the three ipsilateral recurrences detected within the first year of follow up were detected by mammography alone<sup>20</sup>. In the remaining cases, ipsilateral recurrence was detected by physical examination or physical examination and diagnostic mammography.

In the large cohort study, 24.0% to 36.9% of recurrences detected in women who had undergone BCS were detected by surveillance mammography alone. Surveillance mammography alone detected 20.1% to 36.6% of the contralateral breast cancers in women who had undergone mastectomy<sup>11</sup>. As data on the side of the primary cancer and recurrence was not available for the cohort study, the authors of this study were unable to differentiate



Table VI – Studies on surveillance mammography

| Source                       | Level of Evidence | No. of cases in Series (No. with CBC or IR) | Stage at initial diagnosis                | Initial treatment                                 | Years to recurrence                                   | Mammography regimen                                      | Detection rate by mammography alone                                            |
|------------------------------|-------------------|---------------------------------------------|-------------------------------------------|---------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------|
| Ashkanani 2001 <sup>47</sup> | III               | 695 (IR: 21) (CBC: 2)                       | Not Reported, included patients with DCIS | BCT: 100%<br>RTx: Not Reported                    | Mean: 3.5 (Range 2 – 7)                               | Annual Bilateral                                         | 48% (10 of 21)                                                                 |
| Churn 2001 <sup>48</sup>     | III               | 505 (IR: 25) (CBC: Not Reported)            | pT1-3 pN0-1 Nxm0                          | BCT: 100%<br>RTx: 100%<br>CTX: 16%<br>HTx: 90.3%  | Not Reported<br>Annual Hazard rate over 5 years of 1% | No Set Protocol<br>Usually less frequently than annually | 28% (7 of 25)                                                                  |
| Paszat 2001 <sup>11</sup>    | II-2              | 12279 (CBC & IR not reported)               | Invasive Breast Cancer                    | BCT: 60.5%<br>RTx: 41.7%<br>CTX: 21.4%            | Not Reported                                          | Median 4 in 5 Years                                      | BCS - 24.0 - 36.9% (includes both IR & CBC)<br>Mastectomy - 20.1 - 36.6% (CBC) |
| Weight 2002 <sup>20</sup>    | III               | 1151 (IR: 48) (CBC: Not Reported)           | DCIS and Stage I or II                    | BCT: 100%<br>RTx: 89.9%<br>CTX: 18.7<br>HTx: 75.1 | 1 year*                                               | Annually for 2 years, then biennial                      | 66% (2 of 3)*                                                                  |

Level II-2 evidence refers to cohort or case-control analytic studies, preferably from more than one centre or research group

Level III evidence refers to evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees<sup>45</sup>

\* Only 1 year of follow - up of patients whom they report recurrences detected by mammography

Abbreviations: IR – Ipsilateral Recurrence, CBC – Contralateral Recurrence or new primary, BCS – Breast Conserving Surgery, RTx – Radiotherapy, CTx – Chemotherapy, HTx – Hormone Therapy, DCIS – Ductal Carcinoma in situ.

between ipsilateral recurrence and contralateral breast cancers in women who had undergone BCS.

### *2.3.2 Part 2: Surveillance mammography among women with breast reconstruction following treatment of primary breast cancer*

Table VII shows the primary data abstracted from each study in Part 2. Due to the paucity of literature addressing the role of surveillance mammography in women who have undergone breast reconstruction, all articles, including case reports, were considered. In total, eight articles addressed this issue<sup>4, 38-41, 48-50</sup> including two case reports, five case series, and a retrospective case series with imprecise numbers and follow up<sup>41</sup>. One series was a German language article where data was abstracted from the English abstract<sup>48</sup>. Four of the papers included patients with implant based reconstruction and five included patients with autologous reconstructions. Only one paper described the mammography regimen, which consisted of semi-annual mammograms<sup>49</sup>. Only two studies reported local recurrences detected by surveillance mammography or by other means<sup>39, 40</sup>.

Helvie et al. found that two of the three cases of local recurrence in their series of women with TRAM flap breast reconstruction were detected by surveillance mammography, while the third was a palpable breast nodule<sup>39</sup>. In their descriptive study of women with local recurrence in TRAM flap breast reconstruction, Salas et al. report that three cases of local recurrence were detected by diagnostic mammograms, while one case was detected by a surveillance mammogram<sup>40</sup>. Heinig et al. report that 8 of 13 local recurrences in women with silicone implant based breast reconstruction were detected by clinical exam and conventional imaging, but it was not reported how many were detected by mammography

Table VII – Studies on mammography following breast reconstruction

| Source                    | Level of Evidence                             | No. of cases in Series (No. with CBC or IR) | Stage at initial diagnosis                       | Initial treatment                                                                                    | Type of Reconstruction                                            | Years to recurrence Median                 | Mammography regimen                                                         | Detection rate by mammography alone                   |
|---------------------------|-----------------------------------------------|---------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------|
| Dowden 1992 <sup>41</sup> | Case series (III)                             | Approximately 180 (IR: 3)                   | Not reported                                     | Modified Radical Mastectomy                                                                          | Immediate Submuscular Implant                                     | 1 Year<br>3 Years<br>2 Years               | Not Described                                                               | 3/3                                                   |
| Fajardo 1993 <sup>4</sup> | Case series (III)                             | 80 (IR: 1; Silicone Implant)                | Not reported for reconstruction cases            | Mastectomy                                                                                           | Implants (65)<br>Autologous (19)<br>Bilateral Reconstructions (4) | Not reported for reconstruction cases      | Frequency not described                                                     | 0/1                                                   |
| Mund 1994 <sup>50</sup>   | Case report                                   | 1                                           | Stage II                                         | Modified Radical Mastectomy                                                                          | Delayed TRAM                                                      | 7 Years                                    | 3 mammograms in 7 Years                                                     | 1/1                                                   |
| Salas 1998 <sup>40</sup>  | Case series (III)                             | 4                                           | DCIS                                             | Modified Radical Mastectomy (1)<br>Total Mastectomy (3)<br>Contralateral Prophylactic Mastectomy (4) | Immediate TRAM                                                    | 10 Months<br>3 Years<br>2 Years<br>4 Years | Not Described Surveillance<br>Mammography (1)<br>Diagnostic Mammography (3) | 1/4                                                   |
| Helvie 1998 <sup>38</sup> | Case series (III)                             | 6                                           | DCIS                                             | Mastectomy                                                                                           | TRAM                                                              | 42 Months                                  | Only 1 patient underwent mammographic surveillance                          | 1/6                                                   |
| Clark 1999 <sup>49</sup>  | Case report                                   | 1                                           | DCIS                                             | Total mastectomy and Prophylactic Contralateral Mastectomy                                           | Delayed Submuscular Implant                                       | 3.5 Years                                  | Semi-Annually                                                               | 1/1                                                   |
| Helvie 2002 <sup>39</sup> | Case series (III)                             | 113 (IR: 3)                                 | Not reported, included prophylactic mastectomies | Mastectomy                                                                                           | Immediate or delayed TRAM                                         | All greater than 5 years                   | None                                                                        | 2/3                                                   |
| Heinig 1997 <sup>48</sup> | Inadequate description of methods in abstract | 169 (IR: 13)                                | Not Reported                                     | Mastectomy                                                                                           | Silicone Implant                                                  | Not reported                               | Not Reported                                                                | Not reported which were detected by mammography alone |

\* German language, data abstracted from translated abstract

Level III evidence refers to evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees<sup>45</sup>.

Abbreviations: IR – Ipsilateral Recurrence, DCIS – Ductal Carcinoma in situ, TRAM – Transverse Rectus Abdominus Myocutaneous flap

alone<sup>48</sup>. Fajardo reported on the follow up of 80 patients with breast reconstruction, only one of whom developed a local recurrence and it was not detected by surveillance mammography<sup>4</sup>. The remaining studies present individual cases of local recurrence that were detected by surveillance mammography, without providing follow up information regarding local recurrences detected by other means.

## 2.4 *Discussion*

The systematic review of all relevant literature regarding the use of surveillance mammography among women following treatment for primary breast cancer, including those who had undergone mastectomy and breast reconstruction, revealed extensive heterogeneity among the studies in terms of design, follow-up, and mammography regimen. Therefore, the data should not be synthesized in a meta-analysis. Because of this, a narrative discussion ensues.

### 2.4.1 *Surveillance mammography following treatment of primary breast cancer*

There have been five randomized controlled trials addressing follow-up strategies for breast cancer, however these studies did not evaluate the role of surveillance mammography among the enrolled patients<sup>51-55</sup>. Annual mammograms were included as part of the surveillance of patients in both the control and experimental arms in all of these studies. Therefore, these were not included in this review of literature regarding surveillance mammography following treatment of primary breast cancer. No randomized controlled trials were found in either the original systematic review on surveillance mammography following the treatment of primary

breast cancer<sup>5</sup>, or in this update. At the time of publication of the original review, the level of evidence informing clinicians regarding the use of surveillance mammography was II-2 or III. All studies identified in this update of the original systematic review are again level II-2 or III. Despite the lack of level I evidence, the cohort studies and case series addressing this topic have consistently demonstrated the clinical value of surveillance mammography among women treated for primary breast cancer. This value is seen in the number of cases of ipsilateral recurrences or contralateral new breast cancers detected by surveillance mammography alone, ranging from 8% to 50% of ipsilateral recurrences<sup>11, 18, 23, 46, 47, 56-63</sup> and 8% to 87% of contralateral breast cancer recurrences<sup>11, 56, 58, 59, 62, 64-68</sup>. In addition to being detected earlier, recurrences detected by mammography alone are smaller and have less invasive characteristics than recurrences detected by physical examination<sup>18, 23</sup>. There is no good evidence, however, of the effects of surveillance mammography on survival.

#### *2.4.2 Surveillance mammography among women with breast reconstruction following treatment of primary breast cancer*

The mammographic appearance of recurrent carcinoma in autologous tissue reconstructions is similar to that of primary breast cancer<sup>38</sup>, and proponents of surveillance mammography feel that screening breast cancer patients with autologous tissue reconstruction can detect non-palpable cancer before clinical examination<sup>39, 40</sup>. Others feel that mammography is indicated only in patients who present post-operatively with suspicious physical findings<sup>42</sup>. This systematic review found only level III evidence (opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees) at best in

terms of guiding the clinician in the management of these patients. There is no well designed cohort study or randomized controlled trial addressing this issue, and only one of the papers identified described the mammography regimen<sup>49</sup>. Further, while a number of the papers questioned the economic impact of mammographic surveillance in this population, none evaluated this issue. The papers identified, did however, demonstrate that cases of local recurrence can be detected by surveillance mammography in women with breast reconstruction following mastectomy, and that more research is needed in this area to guide clinicians in the management of these patients.

The first report in the literature of local breast cancer recurrence detected in a reconstructed breast was in 1992 in a paper by Dowden<sup>41</sup>. This was a case report of one plastic surgeon who advised his patients who underwent an implant based breast reconstruction following mastectomy to have mammograms of their reconstructed breast. In the three years following this change in his practice, he observed three cases of local recurrence in the reconstructed breasts that were diagnosed by surveillance mammography. Dowden estimated that 180 of his patients had mammograms during this time, but the frequency of mammography was not described. While this observation led him to advise his patients to participate in surveillance mammography of their reconstructed breasts, he also questioned the cost effectiveness of such surveillance. Despite the poor methodology of this report, it is an important paper as it was the first to report cases of local recurrence following breast reconstruction detected by surveillance mammography.

In 1993, Fajardo, Roberts and Hunt published a retrospective case series evaluating the role of mammography of the mastectomy site<sup>4</sup>. This series included patients with and

without breast reconstruction. Those with reconstruction consisted of 65 implant based reconstructions and 19 autologous reconstructions. Four patients had bilateral breast reconstructions, for a total of 80 women with reconstruction. Only one woman with reconstruction developed a local recurrence, which was not detected by surveillance mammography. The frequency of surveillance mammography was not reported, nor was it clear whether these patients had undergone surveillance mammograms or diagnostic mammograms. It is also important to note that this study included only women who underwent mastectomy at a single institution and had mammography of the reconstructed site at the same institution. These inclusion criteria represent a significant potential bias as women who sought care elsewhere would not be included in this study. Further, the lack of definitions of surveillance mammography versus diagnostic mammography raises questions about the finding that mammography did not reveal any recurrences that were not suspected on physical exam.

The first report in the literature describing the detection of a local recurrence in an autologous breast reconstruction appeared in 1994<sup>50</sup>. Over seven years following breast reconstruction with a TRAM flap, one patient underwent 3 surveillance mammograms. The last of these revealed a non-palpable mass which was diagnosed as a local recurrence of her breast cancer. This case report was important as it showed the possibility of detecting a local breast cancer recurrence in an autologous reconstruction with surveillance mammography. There was no discussion in this report about the number of patients treated by the authors or their institution, leaving one to question how common such an event could be in practice.

A German article published in 1997 evaluated the role of MRI in the diagnosis of locally recurrent breast cancer in women with silicone implant based reconstruction<sup>48</sup>. In a comparison between MRI and conventional imaging (mammography and ultrasound), it was found that conventional imaging along with physical examination detected 8 of 13 local recurrences in 169 women with silicone implant base breast reconstruction. The study did not describe how many were detected by mammography alone.

Another case series appeared in the literature in 1998 reporting local breast cancer recurrences detected by mammography<sup>40</sup>. This report describes four patients initially treated for DCIS who then developed local recurrence within TRAM flap breast reconstructions. Of these four cases, three underwent mammography following clinical suspicion of recurrence on clinical examination (i.e. they had diagnostic mammograms) and one had a local recurrence detected by surveillance mammography. The three patients who were diagnosed with local recurrence following suspicious clinical examination did not participate in a follow up program which included surveillance mammography of the reconstructed breast. The identification of another patient with an autologous breast reconstruction who had a subclinical local recurrence detected by surveillance mammography further contributes to the knowledge that these recurrences can indeed be identified by surveillance mammography. This leads one to wonder if the other three patients in this case series might have been identified earlier as having a local recurrence if they had participated in regular surveillance mammography. Despite the identification of a patient diagnosed with a local recurrence by surveillance mammography, the authors question the cost-effectiveness of routine



mammographic surveillance of these patients because recurrences within autologous breast reconstructions are uncommon.

Another case series of women with TRAM flap reconstructions following mastectomy for breast cancer appeared in the literature in 1998<sup>38</sup>. This series consisted of 7 women treated for local recurrence in a TRAM flap reconstructed breast at a single institution. Routine surveillance mammography of TRAM flap reconstructed breasts is not performed at this institution, only diagnostic mammography following suspicious clinical examination. Of these 7 patients, mammography was done prior to surgical management of the local recurrence in 6, and these 6 women made up the study group. All 6 of these patients were originally treated for extensive or multi-focal DCIS. Only 1 of these 6 patients had their local recurrence diagnosed by surveillance mammography, the remaining 5 presented with a palpable lump in their reconstructed breast. The lone patient whose local recurrence was detected by surveillance mammography was followed at another institution, where surveillance mammography was available. Upon review of the mammograms of these 6 patients by 3 radiologists, there were no false negative evaluations. The local recurrences appeared as either a mass or a calcification or both. Further, the recurrent breast cancers were described as appearing similar to those seen in primary breast cancer. Two of the patients diagnosed with local recurrence by diagnostic mammography were found to have lymph node involvement, while the patient who was diagnosed with local recurrence by surveillance mammography was found to be free of lymphatic spread. As routine surveillance mammography is not offered at this institution, it is questioned whether a surveillance program including surveillance mammography would have resulted in earlier

detection of the locally recurrent disease of the 5 patients who presented with a palpable lump on physical exam. As a result of this series of patients, the institution involved has established surveillance mammography as part of its routine follow-up for all patients with TRAM flap breast reconstruction.

Another case report was published in 1999, this time involving a woman with DCIS treated by mastectomy and reconstruction with a saline implant, was published reporting a local recurrence in a reconstructed breast detected by surveillance mammography<sup>49</sup>. The patient in this report underwent semi-annual physical examination and surveillance mammography following her breast reconstruction. Almost three years following her reconstruction a recurrence was detected by surveillance mammography, not by physical examination. This was the first reported case of a local recurrence detected by surveillance mammography in an implant based reconstruction since Dowden published the original observation that mammography could detect local recurrences in these women. The authors of this report go on to recommend mammographic surveillance of women with breast reconstruction who have a strong family history of breast cancer or who are felt to have more than 5% of their breast tissue still present after mastectomy. Studies have shown that 20% to 59% of mastectomy sites contain residual breast tissue, indicating that breast tissue often exists following mastectomy<sup>26, 28</sup>.

The most recent study in the literature addressing the role of surveillance mammography in women with breast reconstruction was published in 2002<sup>39</sup>. In this study, 214 consecutive surveillance mammograms, were evaluated in 113 women at a single center. The decision to undergo surveillance mammography was made clinically by the patient's

treating physician. Of the six patients who had suspicious mammograms and went on to have a biopsy, two were found to have a local recurrence. One patient with a suspicious mammogram did not have a biopsy, as she was diagnosed with metastatic disease. Follow up beyond the study period identified two other patients for whom local recurrence was detected by mammography alone. Two patients in the study group went on to develop recurrences that were detected by physical examination. There was one false negative mammogram. The positive predictive value, sensitivity and specificity were calculated to be 33%, 67% and 98% respectively. The major shortcomings of this study were that it did not include women with implant based reconstruction and it only included women who pursued their follow up and mammographic surveillance at their institution. Further, there was no attempt to address the economic impact of including surveillance mammography in the routine follow up, nor did it address the question of whether earlier diagnosis of local recurrence has an impact on long term survival.

## 2.5 *Conclusions*

With the prevalence of breast cancer survivors increasing, clear guidelines are required for their follow up, including the use of appropriate surveillance mammography. Despite the lack of level I evidence, the cohort studies and case series addressing the use of surveillance mammography following treatment for primary breast cancer have consistently demonstrated its clinical value. The first part of this systematic review, which included all breast cancer patients and not only those who had undergone breast reconstruction, has added recent literature to the original systematic review. This has consolidated the evidence indicating the

need for surveillance mammography following the primary treatment of breast cancer to detect ipsilateral recurrence and contralateral new breast cancers. The effect of surveillance mammography on long term survival remains an area in need of further study.

Not only is the prevalence of breast cancer survivors increasing, but the number of women pursuing breast reconstruction is increasing as well. With this increase clearly documented<sup>29-32</sup>, evidence guiding the follow up of these patients is required. This systematic review has demonstrated a lack of evidence and highlighted the need for a well designed population based cohort study or randomized controlled trial, as well as an economic analysis, to evaluate this issue.

### **3.0 Chapter 3 – Cohort Study**

#### *3.1 Chapter overview*

This section of the thesis analyzes a population based cohort of women in Ontario whose treatment for primary breast cancer included breast reconstruction. In this cohort, analysis of patterns of practice of surveillance mammography showed: (1) there was no consistently identifiable surveillance mammography regimen for women with breast reconstruction, and (2) uncertainty among clinicians and patients regarding the use surveillance mammography for women with breast reconstruction was found, as 39% of the women in the cohort with breast reconstruction had at least one surveillance mammogram of their reconstructed breast. Due to the paucity of events in the cohort (development of local recurrence within a reconstructed breast) it was decided not to perform statistical analysis to test the hypotheses as the results would be of minimal value.

#### *3.2 Study Design and Methods*

##### *3.2.1 Target Population*

The target population for this study is all women in Canada with early stage breast cancer who have undergone mastectomy and chosen to have breast reconstruction.

##### *3.2.2 Study Population*

This study was conducted using an Ontario population-based case-cohort derived from the Ontario Cancer Registry enriched with chart and mammographic review. This enriched

cohort was previously assembled using stratified random sampling as part of a parent study evaluating surveillance mammography. The original cohort, upon which the enriched cohort is based, consisted of 12 279 women who were diagnosed with invasive breast cancer in Ontario between 07/01/91 and 06/30/96. These women were followed until death or 12/31/01, whichever came first. This parent study, funded by the Canadian Breast Cancer Research Alliance (CBCRA) is entitled 'A population based study of the outcome of surveillance mammography after the treatment for primary breast cancer' with principle investigator Lawrence Paszat and co-applicants Eva Grunfeld, Susan Bondy, Douglas Coyle et al<sup>11</sup>.

The enriched cohort included 1526 women from the original cohort. The stratification process for the assembly of the 1526 women included in the enriched cohort was in part based on initial surgical management. Of the 12 279 women in the parent study, 38.7% underwent mastectomy as their initial surgical management. As a result, it was expected that there would be close to 600 women in the enriched cohort who underwent mastectomy as their initial surgical management. It was also expected that a proportion of women who underwent lumpectomy as their initial surgical management would subsequently undergo mastectomy, adding to the sample size. With the rate of breast reconstruction following mastectomy in Ontario being 7.9%<sup>14</sup>, it was expected that the cohort would include over 45 women with breast reconstruction following initial treatment with mastectomy as well as others who were treated initially with lumpectomy but who went on to undergo mastectomy. Over the 10-year study period, it was expected that there would be at least 4 cases of local recurrence in the reconstructed breast. It was recognized that this would result

in an underpowered cohort to test the hypotheses, however it was expected that the data obtained will be the best available for inputting into the economic model in Chapter 4.

### *3.2.3 Operational Definition and Description of Breast Reconstruction*

Breast reconstruction was defined as any reconstructive procedure of the ipsilateral breast which results in a breast mound following mastectomy. All types of breast reconstruction were included in this study. Revision of the mastectomy scar was not considered a breast reconstruction procedure. Reconstructive procedures performed following mastectomy include both autologous (using the patients own tissue) and implant based methods. (Please refer to the glossary for a description of the various breast reconstruction procedures.)

### *3.2.4 Operational Definition of Surveillance Mammography*

Surveillance mammography was defined as previously described. All mammograms in Ontario are performed in public hospitals or in private radiology clinics, and no mammography is performed at cancer centres in Ontario. All mammography except screening mammography is billed to the Ontario Health Insurance Plan (OHIP), the universal health care payer in the province of Ontario, by the radiologist. Only if patients move permanently outside of Ontario, and change their provincial universal health insurance carrier, will mammograms of interest be missed by reviewing the OHIP database.

The first surveillance mammogram for each woman was defined as the first OHIP mammogram billing record dated six months or later following the diagnosis of primary breast cancer. Subsequent surveillance mammograms for each woman were identified as

billing records for mammograms dated at least 11 months since the most recent previous mammogram, and without a billing record for breast ultrasound, biopsy, lumpectomy or mastectomy within the month preceding the mammogram or on the same date. All other mammography billing records for each woman were deemed to represent diagnostic mammograms performed because of clinical findings or to follow up mammographic abnormalities<sup>11</sup>.

It is important to recognize that no mammograms of interest are conducted through the Ontario Breast Screening Program (OBSP), since women with breast cancer are excluded from the OBSP.

### 3.2.5 *Methods*

Using the above mentioned enriched cohort from the parent study, women who have undergone mastectomy and breast reconstruction were identified using the OHIP codes for reconstructive breast procedures (Appendix A). This sample was then examined for surveillance mammograms that had been interpreted as positive. The information for each mammogram was obtained from copies of the original reports. For each positive surveillance mammogram it was planned to describe all breast investigations (additional mammogram, breast ultrasound, breast MRI, biopsy or repeat clinical examination) conducted subsequent to the mammogram to provide an assessment of the consequence of a positive mammogram. The positive and negative predictive values of surveillance mammograms in this group of women were to be calculated. The number of recurrences



detected by surveillance mammography was also determined. See Appendix B for a schematic representation of the cohort analysis.

### *3.2.6 Statistical Analysis*

#### *3.2.6.1 Descriptive Statistics*

Descriptive statistics were used to describe the sample of women from the enriched cohort who had undergone breast reconstruction. Variables described included age, stage of breast cancer at initial diagnosis, initial surgical management, subsequent surgical management, and length of follow up. Length of follow up was reported as both follow-up post diagnosis of breast cancer and follow-up post breast reconstruction. Length of follow up was determined by using the most recent clinical information available as the end point of follow up, and these included the latest mammography, the date of reconstruction or the date of diagnosis of recurrence. The number of women initially treated with lumpectomy who underwent radiotherapy was also described. Due to privacy policy at the Institute for Clinical Evaluative Sciences, cell counts of less than five patients must be reported as “less than five”.

#### *3.2.6.2 Planned Statistical Analysis*

For all hypothesis testing, a p-value of less than 0.05 was to be used as a cut off for statistical significance. To test the first hypothesis, that surveillance mammography detects local recurrence earlier than clinical examination and use of diagnostic mammography in women with breast reconstruction, the null hypothesis is that there is no difference between

the two groups. If statistical significance was achieved in the hypothesis testing, this null hypothesis would have been rejected and it would have been concluded that a difference exists in the cohort that is greater than expected between the two groups due to chance alone. The number of recurrences detected, size of recurrence detected and mortality was to be compared between the two groups using the Chi square test with a Yates correction, or Fisher's exact test if cell counts were less than five. The Yates correction is used when the data to be analyzed is in a 2X2 table, as there is only one degree of freedom. In this case, Fisher's exact test is the appropriate test when cell counts are less than five<sup>69</sup>. The time of recurrence detection since mastectomy was to be compared using a two tailed t-test.

The second hypothesis, that false positives are more common in surveillance mammograms than in diagnostic mammograms among women with breast reconstruction, was to be tested by examining the number of diagnostic procedures, such as biopsy, yielding negative results following suspicious surveillance mammography and comparing this to the number of diagnostic procedures yielding negative results following suspicious diagnostic mammography. The null hypothesis is that there is no difference between rates of false positives in these two groups. These proportions were to be tested using the Chi square test with the Yates correction, or Fisher's exact test if cell counts were five or less.

To test the third hypothesis, that false negatives are more common in surveillance mammograms than in diagnostic mammograms among women with breast reconstruction, the group of women with breast reconstruction who developed a recurrence in the reconstructed breast was examined. A false negative test is one that is interpreted as being negative (normal) when the disease is present<sup>70</sup>. A false negative surveillance mammogram

is defined as a surveillance mammogram performed on a woman with a history of treatment for primary breast cancer that is interpreted as negative when in fact there is a new or recurrent breast cancer present. The operational definition of false negative mammograms in this cohort study included all mammograms interpreted as negative within the 12 months prior to the diagnosis of recurrence. This may lead to an overestimate of false negative results, as the new or recurrent breast cancer may not in fact have been present at the previous mammogram within the 12 months prior to the diagnosis of recurrence. It was decided to use this proxy for false negativity, as without performing mammography on women with known local recurrence it is impossible to truly calculate the rate of false negative studies. The rates of false negatives were to be compared between surveillance and diagnostic mammograms using the Chi square test with the Yates correction, or Fisher's exact test if the cell counts were too small for the Chi-square test to be valid. The null hypothesis is that there is no difference in the rates of false negatives between the two groups.

In the event that there are no events of interest (local recurrence within the reconstructed breast detected by surveillance mammography), hypothesis testing will not be performed. Although the calculations would be possible, the results would be of minimal, if any, value.

### 3.3 *Results*

#### 3.3.1 *Description of cohort*

A total of 55 women in the enriched cohort (55/1526; 3.6%) underwent mastectomy followed by breast reconstruction. Of these, 33 were initially treated with mastectomy, and 22 were initially treated with lumpectomy, and then went on to have mastectomy at a later date. Descriptive statistics including age, stage, type of initial treatment and type of reconstruction can be seen in Tables I - II. To satisfy reporting criteria of the agency that provided the data, stages were combined into two groups to avoid reporting cell counts less than 5. As Stage II and lower are clinically referred to as early stage breast cancer, Stage Tis, I and II were combined into a single group “Early Stage Breast Cancer” while a second group consisted of patients with advanced and unknown stage breast cancer.

#### 3.3.2 *Description of mammography within the cohort*

Detailed information pertaining to mammographic evaluation was available for 38 women within the cohort, who underwent a total of 280 mammograms. The median length of follow up for women with mammographic information was 78.5 months post diagnosis of breast cancer (Range 7 to 124) and 23.5 months post breast reconstruction (Range 0 to 109). Of these 38 women, all had at least one mammogram of their contralateral breast while 15 (39%) underwent at least one mammogram of their reconstructed breast. Of the 15 women who underwent initial treatment with BCS, 12 (80%) underwent at least one surveillance mammogram of the ipsilateral breast prior to mastectomy and reconstruction. The average number of surveillance mammograms of the contralateral breast per year among women in

Table I – Age and stage of disease of women in the study sample

|                                                             |                |    |
|-------------------------------------------------------------|----------------|----|
| Number of women in cohort with breast reconstruction        | 55             |    |
| Women initially treated with lumpectomy                     | 22             |    |
| With radiation                                              |                | 15 |
| Without radiation                                           |                | 7  |
| Women initially treated with mastectomy                     | 33             |    |
| Mean age (years)                                            | 46.7 (SD 11.0) |    |
| Mean age of women initially treated with lumpectomy (years) | 47.4 (SD 11.9) |    |
| Mean age of women initially treated with mastectomy (years) | 46.3 (SD 10.6) |    |
| <b>Stage of Disease</b>                                     |                |    |
| Early stage breast cancer (Tis, I and II)                   | 44             |    |
| Advanced and unknown stage breast cancer                    | 11             |    |

Table II – Description of breast reconstruction in the study sample

|                                                   |                |                                      |                   |
|---------------------------------------------------|----------------|--------------------------------------|-------------------|
| <b>Breast reconstruction</b>                      |                |                                      |                   |
| Number of Delayed Reconstructions*                | 46             |                                      |                   |
| Time to reconstruction (months from mastectomy)   | Median 28.5    | (Range 1 – 130<br>Mean 32.6 SD 33.0) |                   |
| Number of Immediate Reconstructions               | 9              |                                      |                   |
|                                                   |                | <b>Initial Treatment</b>             |                   |
| <b>Type of Reconstruction</b>                     | <b>Total</b>   | <b>Lumpectomy</b>                    | <b>Mastectomy</b> |
| Autologous                                        | 16             | 9                                    | 7                 |
| Implant                                           | 20             | 6                                    | 14                |
| Implant and Autologous                            | 19             | 7                                    | 12                |
| <b>Mean age by Type of Reconstruction (years)</b> |                |                                      |                   |
| Autologous                                        | 46.4 (SD 7.3)  |                                      |                   |
| Implant                                           | 50.2 (SD 14.9) |                                      |                   |
| Implant and Autologous                            | 43.4 (SD 7.7)  |                                      |                   |

\*Delayed reconstructions are breast reconstructions that are performed at a later date than the mastectomy.

this cohort was 0.62, or one surveillance mammogram every 1.60 years. The average number of mammograms per year of the ipsilateral side prior to breast reconstruction among women initially treated with BCS was 0.54, or one surveillance mammogram every 1.84 years. Finally, the average number of surveillance mammograms per year of reconstructed breasts was 0.31, or one surveillance mammogram every 3.18 years.

The 15 women with surveillance mammograms of their reconstructed breasts had a total of 37 mammograms of their reconstructed breasts, less than 5 of which were diagnostic mammograms. The mammograms that were deemed to be diagnostic were classified as such due to the fact that they occurred less than 11 months following the previous mammogram of the same breast. A summary of the number and type of mammograms can be seen in Table III.

There were no mammograms among reconstructed breasts that were interpreted as positive. Thus there were no follow-up investigations performed as a result of a positive mammogram in a reconstructed breast and no false positive surveillance mammograms. Less than five local recurrences were detected clinically within 12 months of a surveillance mammogram that was interpreted as negative, indicating that the surveillance mammogram yielded a false negative result. Also, less than five local recurrences were detected clinically within 12 months of a diagnostic mammogram that was interpreted as negative, indicating that the diagnostic mammogram yielded a false negative result.

Table III – Mammograms captured in the cohort

| All Mammograms                                 |  | Number of Mammograms | Number of Patients |
|------------------------------------------------|--|----------------------|--------------------|
| Contralateral                                  |  | 163                  | 38                 |
| Ipsilateral                                    |  | 80                   | 23                 |
| Ipsilateral mammogram following reconstruction |  | 37                   | 15                 |
| Total                                          |  | 280                  |                    |

| Number of Post-Reconstruction Ipsilateral Mammograms by Type of Reconstruction |  | Number of Mammograms | Patients with Mammograms of Reconstructed Breast |
|--------------------------------------------------------------------------------|--|----------------------|--------------------------------------------------|
| Autologous                                                                     |  | 13                   | ≤5                                               |
| Implant                                                                        |  | 12                   | ≤5                                               |
| Autologous and Implant                                                         |  | 12                   | 6                                                |
| Total                                                                          |  | 37                   |                                                  |

### 3.3.3 *Statistical Analysis*

To test the time to diagnosis of local recurrence with clinical examination and diagnostic mammography versus surveillance mammography, a two-tailed t-test was planned. The mean time to diagnosis of recurrence with diagnostic mammography was 72.5 months (SD 48.8). Due to the absence of local recurrences detected by surveillance mammography within the cohort, the hypothesis that recurrences would be detected earlier by surveillance mammography than by clinical examination and diagnostic mammography was not tested. Therefore, the null hypothesis was not rejected.

The second hypothesis stated that false positives are more common in surveillance mammograms than in diagnostic mammograms among women with breast reconstruction. To test this hypothesis, the Chi square test with Yates correction or a Fisher's exact test would have been performed if there had been events of interest (false positive surveillance or diagnostic mammograms). As there were no mammographic studies that were interpreted as positive in this cohort, the number of false positive studies in each group was 0 and no hypothesis testing was performed. Therefore, the null hypothesis was not be rejected.

The final hypothesis to be tested in this cohort analysis was that false negative mammograms would be more common among ipsilateral surveillance mammograms than among ipsilateral diagnostic mammograms of women with breast reconstruction. To test this hypothesis, the Chi square test with Yates correction or a Fisher's exact test would have been performed if there had been events of interest (false negative surveillance or diagnostic mammograms). There was the same number of false negative surveillance and diagnostic mammograms. The data addressing this hypothesis is presented in a 2 by 2 table in Table IV. Due to confidentiality requirements, cell counts smaller than 5 could not be reported. As



there were cells with less than 5 observations, the analysis would have been performed using a Fisher exact test instead of a Chi square analysis. Due to the paucity of events and the requirement to report cell counts as  $<5$ , hypothesis testing was not performed. Again, the null hypothesis was not rejected.

Table IV – Rate of false negative surveillance mammograms and rate of false negative diagnostic mammograms

| <b>False negatives in surveillance and diagnostic mammograms of the reconstructed breast</b> |                 |                    |       |
|----------------------------------------------------------------------------------------------|-----------------|--------------------|-------|
|                                                                                              | False Negatives | Not False Negative | Total |
| Surveillance mammograms                                                                      | $<5$            | $>27$              | $>32$ |
| Diagnostic mammograms                                                                        | $<5$            | 0                  | $<5$  |
| Total                                                                                        | $<10$           | $>27$              | 37    |

### 3.4 Discussion

#### 3.4.1 Discussion of surveillance mammography among women with breast reconstruction

This is the first population based cohort that has been used to evaluate the role of surveillance mammography among women who have undergone breast reconstruction following mastectomy for the treatment of primary breast cancer. The cohort used in this study consisted of 55 women who had a history of mastectomy following the diagnosis of primary breast cancer in Ontario between 1991 and 1996 and later went on to have breast reconstruction. These 55 women included all women with a history of mastectomy and breast reconstruction drawn from a larger sample of 1526 women previously assembled for a study evaluating surveillance mammography in Ontario. These 1526 women represent a random sample of all women in Ontario diagnosed with primary breast cancer in the same years stratified by initial surgical management. The average age of the 55 women included in this study was 46.7 years (SD = 11.0), which is consistent with other cohorts of women who have undergone breast reconstruction<sup>31</sup>.

Twenty-two women in the cohort were initially treated with BCS. Of these 22 women, 7 did not undergo adjuvant radiation therapy despite the clear guidelines that BCS is to be performed in conjunction with radiotherapy<sup>71</sup>. Of the 55 women in the cohort, the stage of disease was known for 47, and 80% of the women were diagnosed as stage I or stage II. It has been found in previous reports that women with more advanced breast cancer are less likely to undergo breast reconstruction following mastectomy<sup>29-31, 72</sup>. The literature does not support increased cancer stage being a contraindication to breast reconstruction, as these women can have significant improvements in their quality of life during their remaining time<sup>73, 74</sup>. It can be speculated that women with more advanced breast cancer are less likely to undergo breast reconstruction because of lower rates of referral from their ablative

surgeons, that they are less likely to choose to undergo another procedure with another recovery period, and that they may die from their cancer prior to being able to undergo the reconstructive procedure. Regardless of why women with reconstruction tend to have a lower stage of breast cancer, this group is clearly a selected sample with a much better prognosis than the general population of breast cancer patients, which contributed to the low rate of local recurrence in this cohort.

In the group of women included in this study 36% underwent implant based reconstruction, 29% underwent autologous reconstruction and 35% underwent implant/autologous reconstruction. The proportion of those undergoing an implant based reconstruction was similar to the proportion reported to have undergone the same procedure in a cohort in Nova Scotia (38%)<sup>72</sup>, again showing the similarity of this cohort to others that have been used to evaluate breast reconstruction elsewhere. Women who chose to undergo implant based reconstruction also tended to be older than those choosing to undergo autologous tissue reconstruction, perhaps suggesting that older women prefer an operation with less associated morbidity and a shorter recovery period.

Surveillance mammography is currently recommended as part of the follow up of women who have been treated for primary breast cancer, and this recommendation includes regular imaging of the contralateral breast and of the ipsilateral breast if the patient has not had a mastectomy. In this cohort, 80% of women initially treated with BCS underwent at least one surveillance mammogram of the ipsilateral breast, with an average frequency of one mammogram per 1.60 years. This demonstrates that the guidelines directing physicians to include annual surveillance mammography of the ipsilateral breast in the case of BCS are being adhered to in the majority of cases.

It is interesting to note that, with no guidelines instructing the clinician on the use of mammography of the reconstructed breast, 39% of women had at least one mammogram of their reconstructed breast. This variation in practice clearly demonstrates the uncertainty that exists surrounding the use of this investigation. It has previously been suggested that surveillance mammography would be of more use to women who have undergone breast reconstruction with an implant, as the submuscular placement of the implant projects the deep margin of the resection allowing it to be imaged by the mammogram<sup>41</sup>. This was not seen in our cohort as the mammographic examinations of reconstructed breasts were used for women reconstructed both with and without implants, indicating that clinicians are not more or less likely to obtain surveillance mammograms based on the type of reconstruction.

#### *3.4.2 Comparison of surveillance mammography among women with breast reconstruction to screening mammography of the general public*

Despite its wide acceptance, screening mammography is not a perfect screening examination for breast cancer. It has been reported that up to 25% of radiologically visible cancers are missed by screening mammography<sup>75</sup>. A recent study evaluating the impact of computer aids on the sensitivity and specificity of screening mammography reported the sensitivity to be 0.78 (0.75 to 0.81) for radiologists and the specificity to be 0.84 (0.81 to 0.86), with no improvement found with the use of computer aids<sup>76</sup>. A review of 167 221 screening mammograms in British Columbia found a breast cancer detection rate of 3 per 1000 mammograms. Of these 167 221 mammograms, 10 055 were interpreted as “abnormal” and 505 breast cancers were detected. Thus the positive predictive value can be calculated to be 5%<sup>77</sup>. Due to the small number of women with recurrence in the cohort used in the present study, comparison of sensitivity and specificity between surveillance mammography of

women with breast reconstruction and screening mammography cannot be made. Data presented in a previous case series of surveillance mammograms of breasts reconstructed with autologous tissue showed a sensitivity of 67%<sup>39</sup>, which is lower than that of screening mammography.

### 3.5 *Conclusions*

This study found that 39% of women with breast reconstruction underwent at least one surveillance mammogram of their reconstructed breast with a median follow up time of 23.5 months (Range 0 – 109), demonstrating the clinical uncertainty surrounding surveillance for these women. In this cohort of women no local recurrences were detected by surveillance mammography and none of the surveillance mammograms of the reconstructed breasts were interpreted as a positive study. Moreover, at least one false negative (cell count < 5) was found in both surveillance mammograms and diagnostic mammograms of reconstructed breasts. With this occurrence of false negative exams observed, future research should include an evaluation of other imaging modalities, such as magnetic resonance imaging (MRI) for this group of patients.

It is difficult to suggest a recommendation for the follow up of this group of patients based on the mammographic data of only 38 patients. This cohort study was underpowered to detect a significant difference. It was expected that there would be more cases of local recurrence within the cohort, however this was not the case. In order to have a sample large enough to detect a 10% decrease in metastatic spread (77% risk of metastasis after local recurrence<sup>78</sup> to 69.3%,  $\alpha = 0.05$ ,  $\beta = 0.20$ ) with the use of surveillance mammography among women with breast reconstruction, there would need to be 1036 women in the cohort with

local recurrence of breast cancer following mastectomy and breast reconstruction (sample size calculation made with Epicalc 2000). In order to achieve this with a population based cohort having the characteristics of the one used in this study, there would need to be 527 000 women with a diagnosis of breast cancer in the cohort, with half of them undergoing yearly bilateral surveillance mammography and half of them undergoing yearly surveillance mammography of the contralateral breast only.

Further study and an economic analysis will be required to definitively answer the question of whether these women should routinely participate in a follow up program including surveillance mammography of the reconstructed breast.

## 4.0 Chapter 4 – Economic Evaluation

### 4.1 Chapter overview

An economic evaluation was undertaken to establish the cost-effectiveness of bilateral surveillance mammography following mastectomy and breast reconstruction among women treated for primary breast cancer. This was an exploratory cost-effectiveness analysis from the perspective of the Ontario Ministry of Health, the universal health care payer in the province of Ontario. The threshold of cost-effectiveness was set at \$50 000 per life year gained. It was found that in order to be cost-effective, a relative reduction in metastatic risk of 3.34% for local recurrences detected by surveillance mammography was required compared to those detected clinically. Sensitivity testing demonstrated the relative risk reduction required for cost effectiveness to be similar when the variables were manipulated.

### 4.2 Problem stated

The analysis was conducted with the aim of addressing the following scenario:

Problem stated: A 40 year old pre-menopausal woman with breast cancer undergoes mastectomy and breast reconstruction with or without an implant. Should she undergo surveillance mammography of the reconstructed breast? What relative reduction in metastatic risk following detection of local recurrence by surveillance mammography versus those detected by clinical examination and diagnostic mammography is required for this surveillance program to be cost-effective? The cost effectiveness will be determined by the trade off between the extra costs associated with bilateral surveillance mammography and false positive tests versus the potential reduction in metastatic spread following local recurrence of breast cancer.

### 4.3 *Methods*

This analysis was performed as a cost-effectiveness analysis from the perspective of the Ontario Ministry of Health using a Markov model with three-month periods. A secondary cost-utility analysis was performed. The term utility refers to the quality of life of one health state relative to others. Perfect quality of life would have a utility value of 1, while death would have a utility weight of 0. Cost utility analysis allows for assessment of the quality of life-years gained, not just the crude number of years gained<sup>79</sup>. Threshold values for cost-effectiveness used were \$50 000 per Life Year (LY) gained and \$50 000 per Quality Adjusted Life Year (QALY) gained. There is no established or published threshold for a value of a QALY in Canada. The reasons for this are complex and political: primarily establishment of a threshold will would limit decision makers in terms of the flexibility of having alternative decision rules for different situations. Also, there are strong arguments that adopting a rigid threshold would lead to increasing growth on drug formulary budgets. However, in this analysis a threshold of \$50,000 is adopted as in many other Canadian economic evaluations to reflect the maximum decision makers appear to be willing to accept with respect to new technologies given previous funding decisions<sup>80</sup>. Markov modeling was used as there were a number of possible health states, and movement between many of them was possible. To address the fact that transition probabilities are independent of previous health states experienced by the patient, some of the health states were split according to how the patient arrived in the health state, as well as the length of time spent in the health state (see Section 4.3.1 for further detail)<sup>81</sup>.



#### 4.3.1 *Basic Model*

A Markov model was used to compute the collective outcomes of cohorts of patients treated for primary breast cancer who have undergone mastectomy and breast reconstruction and then followed with and without surveillance mammography of the reconstructed breast. Markov modeling uses transition probabilities between different health states over a set period of time known as the Markov cycle in order to track patients with the condition of interest over time. Each health state is assigned a cost associated with the length of the Markov cycle. Each health state is also assigned probabilities of transition from it to all other health states (including returning to the same health state) during the length of the Markov cycle. These transition probabilities add up to 1 for each health state in each Markov cycle. Markov models are frequently used to analyze diseases and treatments characterized by recurrence of disease states or treatment algorithms<sup>79</sup>. Markov models suffer from the strict assumption of “zero memory”, in that the transition probabilities depend only on the current health state the patient is in, not on how they arrived at the health state or how long they have been there<sup>79</sup>. This assumption of zero memory was addressed in the model by creating multiple similar health states that take into account from where the patient arrived at the health state and how long they have been in the health state. For example, the risk of metastatic spread is greater during the first 1.5 years following local recurrence, and this was incorporated into the model by sequential “Local Recurrence” health states where the transitional probabilities change after being in the sequence for 1.5 years (see section 4.4.5 for further information on transition probabilities following local recurrence). Nine health states were described and can be seen in Table I. Any difference detected between the two groups is due to the presence of the health state “Known Local Recurrence Asymptomatic” in the group who undergo surveillance mammography, as this

health state represents the earlier detection of the local recurrence with the use of surveillance mammography. Although there are costs associated with this state, it is anticipated that people in this state will be less likely to advance to metastatic disease health states than patients who progress to the “Local recurrence, clinically evident” health state (i.e. early detection will decrease the likelihood of metastatic spread). It is this reduction in metastatic risk that will be manipulated in the model to identify a threshold at which surveillance mammography becomes cost-effective. Schematic representations of the two arms of the economic model are shown in Figures 1 and 2. In the model, both costs and effects were discounted at an annual rate of 5%.

Table I – Description of health states included in Markov model

| Health State                           | Description                                                                                                                                                                                                                                                                                                |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. No recurrence                       | Cost of regular follow-up with family physician or oncologist<br>For those patients receiving surveillance mammography, the cost of surveillance mammography program, as well as costs associated with further investigation of positive mammogram<br>Highest expected utility                             |
| 2. Local recurrence asymptomatic       | Cost of diagnosis and treatment of local recurrence plus cost of regular follow up<br>Lower expected utility                                                                                                                                                                                               |
| 3. Local recurrence evident            | Cost of diagnosis and treatment of local recurrence plus cost of regular follow up<br>Lower expected utility (slightly lower than 2)                                                                                                                                                                       |
| 4. No recurrence post local recurrence | Cost of regular follow-up with family physician or oncologist<br><br>For those patients receiving surveillance mammography, the cost of surveillance mammography program, as well as costs associated with further investigation of positive mammogram<br>Higher expected utility than 3, but lower than 1 |
| 5. Diagnosed Metastatic Disease        | Cost of diagnosis and initial treatment of systemic recurrence<br>Lower expected utility                                                                                                                                                                                                                   |
| 6. Treatment of metastatic disease     | Cost of treatment of systemic recurrence<br><br>Lower expected utility                                                                                                                                                                                                                                     |
| 7. Metastatic Disease follow-up        | Cost of follow-up of systemic recurrence<br>Lower expected utility                                                                                                                                                                                                                                         |
| 8. New Death                           | Cost associated with terminal care of a cancer patient<br>Must progress to Death in next cycle<br>No utility value                                                                                                                                                                                         |
| 9. Death                               | Absorbing health state<br>No cost<br>No utility value                                                                                                                                                                                                                                                      |



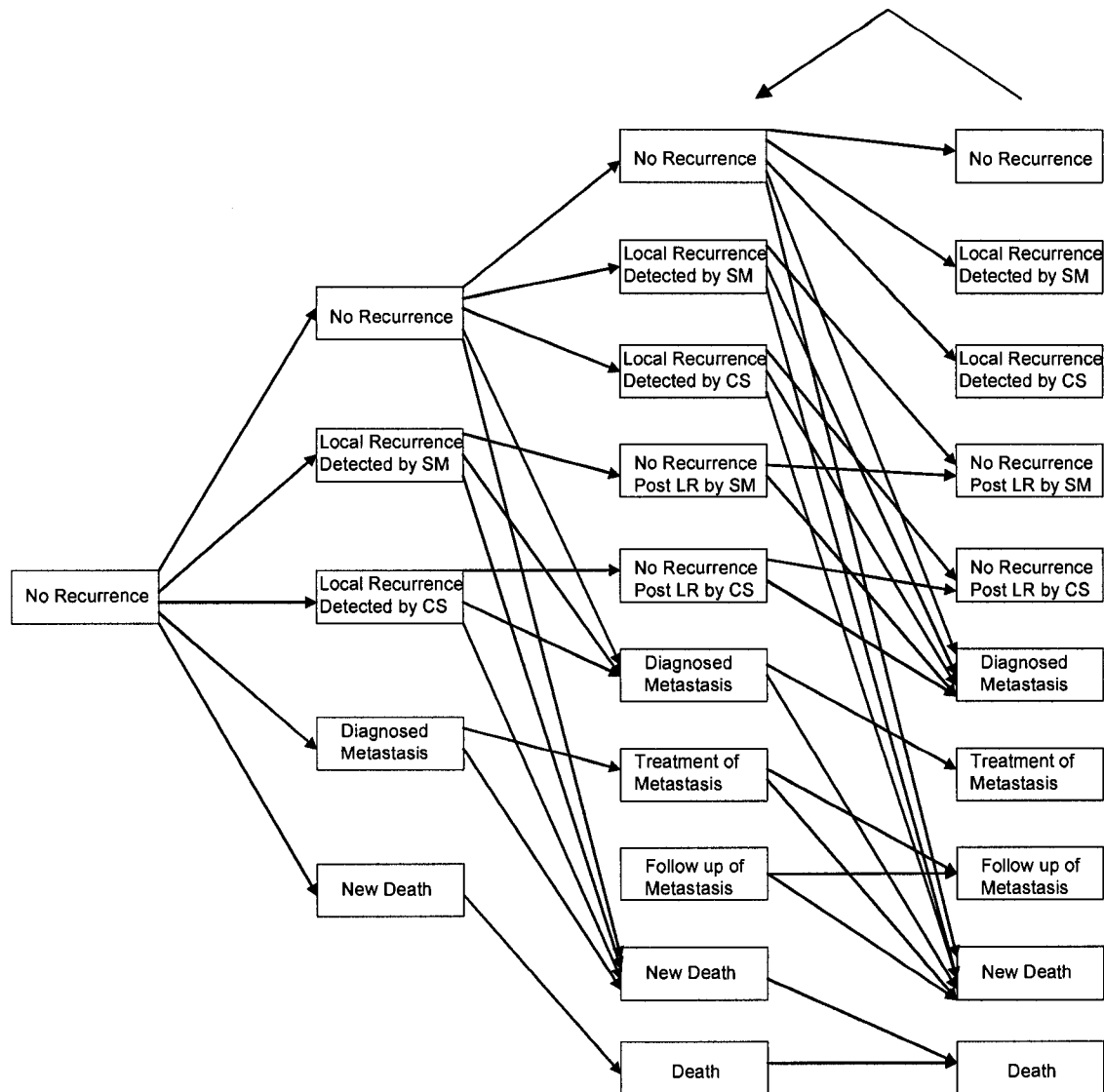


Figure 2 - Schematic representation of Markov model of women with breast reconstruction undergoing bilateral surveillance mastectomy. The last two columns repeat until the model reaches 20 years. SM – Surveillance Mammography, CS – Clinical suspicion, LR – Local Recurrence.

#### 4.3.2 Costing

The costing data was derived from multiple sources. This evaluation is from the perspective of the Ministry of Health, and although societal costs are important, they will not be considered as it is beyond the scope of the thesis to collect societal costs. The analysis adopts a health care system perspective following the Canadian guidelines for economic evaluation developed by Canadian Agency for Drugs and Technologies in Health published in 2006. The guidelines state the perspective "should be that of the publicly funded health care system." The inclusion of societal costs is still an issue of debate particularly as the productivity losses associated with illness tend to be greatly overestimated<sup>82</sup>. Economic analyses taking the perspective of the Ministry of Health consider the costs that are paid by the Ministry of Health only. Societal costs such as time off work, transportation to sites of care, meal costs when away from home and many others are not considered when taking this perspective. The costs of regular follow up were required for both groups of women: those receiving surveillance mammography and those not receiving surveillance mammography. Fee for service fees were used as the actual cost estimate for the follow up visit.

The costing procedure consisted of estimating costs associated with surveillance mammography, including the cost of 1) the mammogram, 2) radiologist fees, 3) personnel costs and 4) overhead costs. Costs for the follow up of positive mammograms will be assigned the cost of diagnosis of local recurrence, as these will be the investigations indicated following a positive surveillance mammogram. Diagnostic mammograms are performed in both private physicians' offices and in hospitals. When performed in a private office, the office is remunerated on a fee for service basis, and this fee can be used as a cost for these tests<sup>83</sup>. The four costs of surveillance mammography listed above are included in this fee, and therefore this fee will be used as the cost for each mammographic procedure<sup>83</sup>.

Although this is only an estimation of these four costs, this fee is the true cost to the Ministry of Health and therefore accurately represents the cost from the perspective being used in this analysis, that of the Ministry of Health.

Diagnostic procedures following a positive mammogram will be either radiological or surgical. Radiological procedures will be costed in the same mechanism as the mammograms were costed above. Treatment and follow-up costs were obtained from the Statistics Canada Population Health Model (POHEM) Breast Cancer Workbook on the Global Costs of Breast Cancer Diagnosis and Management<sup>84</sup>. The cost associated with the diagnosis of a local recurrence was used as an estimate for the cost of testing following a false positive mammogram. Treatment costs for metastatic breast cancer were obtained from a report to Eli Lilly entitled “An Estimate of Breast Cancer Costs for a Decision Analysis Project” prepared by Earle, Coyle, Wells and Papadimitropoulos<sup>85</sup>. These costs were updated with recent Ontario Health Insurance Plan (OHIP) data. The costs within the POHEM workbook and the report to Eli Lilly which were not readily available for update, were inflated by the Canadian Consumer Price Index for Health Care from Statistics Canada to arrive at their value in 2003 Canadian dollars. For costs obtained from the 1996 POHEM workbook, the costs were multiplied by the inflation factor derived from the Canadian Consumer Price Index for Health Care from January 1996 until January 2003 (1.151). For costs obtained from the 1999 report to Eli Lilly, the costs were multiplied by the inflation factor derived from the Canadian Consumer Price Index for Health Care from January 1999 until January 2003 (1.094). The costs of the various health states can be seen in Tables II – VII. The cost of a new death was based on the cost of terminal care of a breast cancer patient being \$1302.56 per week over 13 weeks.

Table II – Costs associated with three months in the health state “No Recurrence” in 2003 Canadian dollars

|                                                              | Year 1         | Year 2         | Year 3         | Year 4         | Year 5         |
|--------------------------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| Mammography                                                  |                |                |                |                |                |
| Bilateral Mammogram                                          | \$14.80        |                |                |                |                |
| Unilateral Mammogram                                         | \$10.50        |                |                |                |                |
| Blood tests                                                  | \$10.14        | \$9.84         | \$8.64         | \$7.17         | \$6.66         |
| F/U Excluding blood tests                                    | \$40.80        | \$35.88        | \$29.55        | \$27.00        | \$25.14        |
| Cost of false positive exam *                                | \$0.56         | \$0.56         | \$0.56         | \$0.56         | \$0.56         |
| <b>Total with yearly bilateral surveillance mammography</b>  | <b>\$66.30</b> | <b>\$61.08</b> | <b>\$53.55</b> | <b>\$49.53</b> | <b>\$47.16</b> |
| <b>Total with yearly unilateral surveillance mammography</b> | <b>\$61.44</b> | <b>\$56.22</b> | <b>\$48.69</b> | <b>\$44.67</b> | <b>\$42.30</b> |

Costs obtained from 2003 OHIP Schedule of Benefits and 1996 POHEM Breast Cancer Workbook

\*The cost of a false positive exam is equal to the cost of diagnosis of a local recurrence, as the same tests are conducted. Therefore, the cost of false positive examinations distributed over all patients in the health state is equal to the proportion of those with false positive exams each year (1%) multiplied by the cost of a single false positive exam (\$222.20, see Table III) divided by the number of Markov cycles in a year (4).



Table III – Costs associated with the diagnosis and treatment of local recurrence following mastectomy in 2003 Canadian Dollars

|                                        | <b>Cost</b>       | <b>Weight</b> |
|----------------------------------------|-------------------|---------------|
| <b>Diagnosis</b>                       |                   |               |
| Diagnostic Costs Excluding Mammography | \$178.90          |               |
| CBC, Biochem                           | \$43.30           |               |
| <b>Total</b>                           | <b>\$222.20</b>   | <b>1</b>      |
| <b>Surgery (Excisional Biopsy)</b>     |                   |               |
| Surgery Consultations and procedure    | \$350.61          |               |
| Assistant and Anesthesia Units         | \$156.73          |               |
| <b>Total</b>                           | <b>\$507.34</b>   | <b>0.5*</b>   |
| <b>Radiation</b>                       |                   |               |
| Physician Costs                        | \$235.60          |               |
| Radiation and CBC costs                | \$4,841.32        |               |
| <b>Total</b>                           | <b>\$5,076.92</b> | <b>0.7*</b>   |
| <b>Chemotherapy</b>                    | <b>\$4,440.83</b> | <b>0.5*</b>   |
| <b>Health State Total</b>              | <b>\$6,250.13</b> |               |

Costs obtained from 2003 OHIP Schedule of Benefits and 1996 POHEM Breast Cancer Workbook

There are no published reports available to provide this data. As such, these weights have been estimated through reading didactic literature on the management of women with breast cancer as well as discussion with clinicians in the fields of medical oncology and reconstructive surgery. As these weights are imprecise, a wide sensitivity analysis will be performed around the cost of this health state.

Table IV – Cost of three months follow up following diagnosis and treatment of local recurrence in 2003 Canadian dollars

|                                                              | Year 1          | Year 2          | Year 3          | Year 4          | Year 5          |
|--------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>Follow up Cost</b>                                        |                 |                 |                 |                 |                 |
| Physician costs                                              | \$108.18        | \$108.18        | \$91.74         | \$91.74         | \$81.45         |
| CBC, Biochem                                                 | \$13.98         | \$13.98         | \$13.98         | \$13.98         | \$13.98         |
| <b>Total with yearly unilateral surveillance mammography</b> | <b>\$136.96</b> | <b>\$136.96</b> | <b>\$120.52</b> | <b>\$120.52</b> | <b>\$110.23</b> |
| <b>Total with yearly bilateral surveillance mammography</b>  | <b>\$132.66</b> | <b>\$132.66</b> | <b>\$116.22</b> | <b>\$116.22</b> | <b>\$105.93</b> |

Costs obtained from 2003 OHIP Schedule of Benefits and 1996 POHEM Breast Cancer Workbook

Table V – Cost of diagnosis and initial three months of follow up of metastatic breast cancer in 2003 Canadian dollars

| Location of Metastatic Spread |             | Weight*  |     |
|-------------------------------|-------------|----------|-----|
| Soft tissue                   |             |          |     |
|                               | Diagnosis   | \$230.04 |     |
|                               | Blood tests | \$44.74  |     |
|                               | Total       | \$274.78 | 0.1 |
| Bone                          |             |          |     |
|                               | Diagnosis   | \$240.70 |     |
|                               | Blood tests | \$44.19  |     |
|                               | Total       | \$284.89 | 0.3 |
| Viscera                       |             |          |     |
|                               | Diagnosis   | \$256.55 |     |
|                               | Blood tests | \$48.56  |     |
|                               | Total       | \$305.11 | 0.6 |
| Health State Total            |             | \$296.01 |     |

Costs obtained from 2003 OHIP Schedule of Benefits and 1996 POHEM Breast Cancer Workbook

\* Weights obtained from Earle, Coyle, Wells and Papadimitropoulos<sup>85</sup>

Table VI – Cost of three months follow up for patients with metastatic breast cancer in 2003 Canadian dollars

|                               | <b>Cost</b>       |
|-------------------------------|-------------------|
| One day in hospital per month | \$1,650           |
| Other services                | \$214.08          |
| <b>Health State Total</b>     | <b>\$1,864.08</b> |

Costs obtained from 2003 data and 1996 POHEM Breast Cancer Workbook

Table VII – Costs associated with three months of treatment of metastatic breast cancer in 2003 Canadian dollars

|             |     |                               |          | 2003         | Weighted cost  |
|-------------|-----|-------------------------------|----------|--------------|----------------|
| Soft Tissue | 10% | Diagnostic surgery            | 79.77    |              |                |
|             |     | Local treatment of Metastasis | 6421.21  |              |                |
|             |     | Systemic treatement           | 4078.77  |              |                |
|             |     | <b>Total</b>                  | 11574.25 | 1157.43      |                |
| Bone        | 30% | Diagnostic surgery            | 1.56     |              |                |
|             |     | Local treatment of Metastasis | 2762.2   |              |                |
|             |     | Systemic treatment            | 1965.75  |              |                |
|             |     | <b>Total</b>                  | 5174.08  | 1552.22      |                |
| Visceral    | 60% | Diagnostic surgery/Procedures | 92.32    |              |                |
|             |     | Local treatment of Metastasis | 4381.95  |              |                |
|             |     | Systemic treatment            | 3694.23  |              |                |
|             |     | <b>Total</b>                  | 8936.34  | 5361.80      |                |
|             |     |                               |          | <b>Total</b> | <b>8071.45</b> |

These costs have been derived from the report to Eli Lilly entitled "An Estimate of Breast Cancer Costs for a Decision Analysis Project" prepared by Earle, Coyle, Wells and Papadimitropoulos. The costs have been inflated from 1999 dollars to 2003 dollars by the Canadian Consumer Price Index for Health Care.

#### 4.3.3 *Sensitivity Analysis*

The economic analysis was designed to determine the minimum relative risk reduction of metastases following diagnosis of local recurrence by surveillance mammography which would lead to the conclusion that surveillance mammography after reconstruction was cost effective. Sensitivity analyses were designed to explore how this value would vary adopting different values for other parameters. If the sensitivity analyses lead to the conclusion that the results do not vary significantly with alternative parameter values, we would have a strong indication of what the minimal relative risk reduction would have to be for surveillance mammography of the reconstructed breast to be cost effective. Transition probabilities and cost estimates were varied across possible values to demonstrate the effect of uncertainty on the results. Factors altered in the sensitivity analysis include the annual rate of local recurrence, the percent of local recurrences detected by surveillance mammography (sensitivity of surveillance mammography), the costs of diagnosis, treatment and follow up of metastatic spread, and the false positive rate of surveillance mammography of reconstructed breasts.

#### 4.3.4 *Secondary Cost-Utility Analysis*

A secondary analysis was conducted using QALY weights derived from a convenience sample of fourteen volunteers, affiliated with the Department of Epidemiology and Community Medicine at the University of Ottawa. Each of the health states was described to the volunteers, and the QALY weights were determined by the use of a visual analog scale (VAS, Appendix C). Volunteers were given the VAS, and asked to draw a line from each health state to a point on the scale representing their perceived value of the quality of life

associated with each given health state. Of the fourteen volunteers, two were male, four were physicians, five were allied health professionals and the remainder were students in the Epidemiology and Community Medicine Program at the University of Ottawa. The QALY weight was the mean value of the health state on the visual analog scales completed by the volunteers (Table VIII).

Table VIII – Utility values used in the secondary cost-utility analysis

| Health State                                     | Utility Value (Mean) | SD    |
|--------------------------------------------------|----------------------|-------|
| No recurrence, asymptomatic                      | 91.07                | 5.25  |
| Local recurrence, asymptomatic                   | 72.50                | 7.78  |
| Local recurrence, clinically evident             | 65.57                | 5.80  |
| Metastatic disease, asymptomatic                 | 41.07                | 15.83 |
| Metastatic disease, symptomatic not in treatment | 23.86                | 10.98 |
| Metastatic disease, symptomatic in treatment     | 18.21                | 11.23 |
| Death                                            | 1.07                 | 4.01  |

#### 4.4 *Summary of Data Used for Analysis*

Although it was planned to use data from the cohort for the population of transition probabilities in the model, these data were insufficient. As such, the literature and clinical judgment were alternative sources of data. Many of the transition probabilities with regards to disease progression were obtained from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) data<sup>86</sup>, which has previously been used by many economic models dealing with breast cancer<sup>81, 87-89</sup>. The sources of data for each of the transition probabilities are summarized in Table IX.

Table IX – Sources of data for the transition probabilities used in the Markov model

| <b>Data</b>                      | <b>Source</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Costing</b>                   | <p>A national list of provincial costs for health care: Canada 1997/8. Institute of Health Economics 2000.<sup>83</sup></p> <p>POHEM Statistics Canada. Breast Cancer Workbook: Global Costs of Breast Cancer Diagnosis and Management. 1996.<sup>84</sup></p> <p>Earle C, Coyle D, Wells G, Papadimitropoulos E. Report to Eli Lilly: An Estimate of Breast Cancer Costs for a Decision Analysis Project. 1999.<sup>85</sup></p>                                                                                                                                                                                                                                                                                                                                |
| <b>Rate of LR</b>                | <p>1% per year, represents a reasonable value within the range of reported values and that seen in the cohort: Kroll SS, Khoo A, Singletary SE, et al. Local recurrence risk after skin-sparing and conventional mastectomy: a 6-year follow-up. <i>Plast Reconstr Surg</i> 1999; 104(2):421-5.<sup>34</sup></p> <p>Langstein HN, Cheng MH, Singletary SE, et al. Breast cancer recurrence after immediate reconstruction: patterns and significance. <i>Plast Reconstr Surg</i> 2003; 111(2):712-20; discussion 721-2.<sup>35</sup></p> <p>Spiegel AJ, Butler CE. Recurrence following treatment of ductal carcinoma in situ with skin-sparing mastectomy and immediate breast reconstruction. <i>Plast Reconstr Surg</i> 2003; 111(2):706-11.<sup>36</sup></p> |
| <b>Rate of metastasis</b>        | <p>Weights of node-negative and node-positive women were taken from the cohort</p> <p>Metastatic rates for node-negative and node-positive women were extrapolated from:</p> <p>Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. <i>Lancet</i> 1996; 348:1189-1196.<sup>86</sup></p>                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>False negative rate</b>       | <p>Cohort</p> <p>Manipulated in the sensitivity analysis</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>False positive rate</b>       | <p>Helvie MA, Bailey JE, Roubidoux MA, et al. Mammographic screening of TRAM flap breast reconstructions for detection of nonpalpable recurrent cancer. <i>Radiology</i> 2002; 224(1):211-6.<sup>39</sup></p> <p>Manipulated in the sensitivity analysis</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Salvage rate following LR</b> | <p>Carlson GW, Styblo TM, Lyles RH, et al. Local recurrence after skin-sparing mastectomy: tumor biology or surgical conservatism? <i>Ann Surg Oncol</i> 2003; 10(2):108-12.<sup>78</sup></p> <p>This was varied for the group undergoing bilateral surveillance mammography to determine a threshold of cost-effectiveness</p>                                                                                                                                                                                                                                                                                                                                                                                                                                  |

#### 4.4.1 *Rate of local recurrence*

The rate of local recurrence among women with breast reconstruction has been reported in the literature to be 2.3% to 7%<sup>34-36</sup> in 6 to 10 years of follow-up. The rate of local recurrence following mastectomy has been shown to be similar to that following BCS<sup>12</sup>, and this rate following BCS ranges in clinical trials from 4% to 11% with follow up ranging from 5 to 12 years<sup>90-97</sup>. There were less than five cases of local recurrence in the 55 women making up the cohort component of this study, with a range of follow up of 5 – 10 years (< 9.1%) consistent with other reports in the literature. For the purposes of the economic analysis, a figure of 1% per year of local recurrence will be used, as this is felt to represent a reasonable value within the range of reported values from both the cohort and others in the literature.

#### 4.4.2 *Metastatic spread*

The data in the cohort was insufficient to provide an appropriate rate of metastatic spread following treatment of primary breast cancer and breast reconstruction. To obtain a probability of metastatic spread, the recurrence rates from the EBCTCG report were extrapolated for both node-negative and node-positive breast cancer patients in five year intervals. It was assumed that the recurrence rates were stable within each of the five year periods, and the 5<sup>th</sup> root of these values was then calculated thereby giving an annual rate of recurrence during each of these five year periods for both node-negative and node-positive breast cancer patients. This was obtained by calculating the yearly risk of not developing metastatic spread and then deriving the yearly risk of developing metastatic spread from this (see example calculation below for X).



In this example, the calculation for yearly metastatic risk during the first five years after diagnosis of node-negative breast cancer is calculated.

$X$  = Risk of metastatic spread over 5 years

$Y$  = Yearly risk of metastatic spread

$X = 16\%$ , or  $0.16$

$1 - X = (1 - Y)^5$

$0.84 = (1 - Y)^5$

$1 - Y = 0.966$

$Y = 0.034$

The yearly risk of metastatic spread for women with node-negative breast cancer is 3.4% during the first 5 years following diagnosis.

The 5<sup>th</sup> root was used, as this rate applied yearly over 5 years results in the known 5 year recurrence rate derived from the EBCTCG report. The weighted averages of these values were then calculated using the proportion of known node-negative (59.6%) and node-positive (40.4%) breast cancer patients within the cohort. The five year recurrence rate of node-negative women was 16.0%<sup>86</sup>, which is a yearly rate of 3.4% if the rate is constant over these five years. The five year recurrence rate for node-positive women was 48.2%<sup>86</sup>, which is a yearly rate of 12.3%. The weighted average of these yearly rates is 7.0%.

3.4% recurrence among node-negative X 59.6% weight + 12.3% recurrence among node-positive patients X 40.4% Weight = 7.0% yearly recurrence rate during first five years

As there is a local recurrence rate of 1% in the model (see Section 4.4.1), The 23% of local recurrences that do not go on to develop metastatic disease<sup>78</sup> was then subtracted from this value for each of the years in order to obtain the annual rate of metastatic spread (see section 4.4.5 for further discussion around the risk of metastatic spread following local recurrence). This produced a yearly probability of 6.77% of metastatic spread during the first five years.

7% recurrence rate - 23% of local recurrences that do not metastasize X 1% local recurrence rate = 6.77% yearly risk of metastasis during first five years

Similar calculations resulted in a risk of metastatic spread of 0.86% during the next five years and 0.93% during years 11-14. One assumption made by the model is that the risk of death for women with metastatic disease is constant, and not related to the length of time since they developed metastases. Further, in the first five years of the model, it is possible for patients to proceed directly to death as early recurrence tends to be more aggressive and may progress to death within a three-month period. After the first five years, the patients in the model must pass through a metastatic disease health state before progressing to death. Patients cannot pass directly from diagnosis of metastatic disease to follow-up of metastatic disease, as these patients must receive initial treatment of metastatic breast cancer prior to progressing to regular follow-up.

#### *4.4.3 False negative rate of surveillance mammography of reconstructed breast*

There were less than five false negative surveillance mammograms, and less than five cases of local recurrences in women who underwent surveillance mammography in the cohort component of this study. As discussed earlier, the precise number cannot be reported due to

ICES privacy regulations. As these are the only data addressing the issue of false negative mammograms following breast reconstruction, it represents the best available data.

Therefore, sensitivity of surveillance mammography will be set at 50% for this analysis, and this will be varied in the sensitivity analysis. Yearly surveillance mammography with a sensitivity of 50% and a local recurrence rate of 1% per year would result in a false negative rate of 0.5%.

$0.01$  (yearly local recurrence)  $\times$   $1$  (surveillance mammogram per year)  $\times$   $.5$  (sensitivity of surveillance mammography of reconstructed breast) =  $0.005$  (0.5%)

#### *4.4.4 False positive rate of surveillance mammography of reconstructed breast*

As there were no mammograms interpreted as positive in the cohort component of the study, this value needed to be obtained elsewhere. The positive predictive value of screening mammography in the general public has been reported to be between 4.4% and 12.2%<sup>43, 77</sup>. Although one might expect the specificity of surveillance mammography of reconstructed breasts to be less than that of screening mammography due to the presence of scarring, surgical clips, implants and fat necrosis, the population is much more at risk (1% per year) and therefore the positive predictive value should be much higher. This is due to the fact that the positive predictive value of a test will vary depending on the prevalence of the disease within the population being tested, even if the sensitivity and specificity remain the same. One case series in the literature has described the sensitivity of surveillance mammography in women with breast reconstruction as 67%<sup>39</sup>. After consideration of the above information, a value for the positive predictive value of surveillance mammography of a post-reconstruction breast has been assigned as 50%, meaning that only half of the surveillance

mammograms interpreted as positive will actually be diagnosed as a local recurrence of breast cancer. With a local recurrence rate of 1% per year and a surveillance regimen including yearly surveillance mammography, this would mean that 1% of all surveillance mammograms will be false positive studies. This will also be varied in the sensitivity analysis in order to determine the its effect on the findings. As false positive exams overtly increase the cost of surveillance mammography, only one-way sensitivity analysis (increasing frequency of false positive exams) will be performed around this value.

#### *4.4.5 Salvage rate of patients diagnosed with local recurrence*

In order to assign a value to the salvage rate of patients with a local recurrence, data from Carlson et al's paper on the follow-up of patients with local breast cancer recurrence following mastectomy and breast reconstruction was used<sup>78</sup>. Salvage rate is used to describe the number of women with local recurrence that are prevented from progressing to metastatic disease. In this paper, it was found that 77% of women with local recurrence following mastectomy and breast reconstruction for the treatment of breast cancer went on to develop metastatic breast cancer. The mean time to metastasis from diagnosis of local recurrence was 19 months, with a range of 2.9 to 61.6 months. Seventy nine percent of the women with metastatic breast cancer following local recurrence went on to die from their breast cancer. In order to calculate yearly risks of progression to metastatic disease, it was assumed that half of the cases of metastatic spread following local recurrence (38.5%) occurred in the first 1.5 years, and the remainder occurred in the next 3.5 years. This assumption was made as the mean time to metastatic spread following local recurrence in this study was 19 months. Based on this assumption, after 1.5 years, 61.5% of the women with local recurrence will not have gone on to metastatic spread. Therefore, the 1.5<sup>th</sup> root of 0.615 (38.5% is half of the

77% that go on to metastatic spread<sup>78</sup>,  $1-0.385=0.615$ ) will give the yearly probability of the event not occurring during the first 1.5 years. This was then used to calculate the yearly risk of the event occurring (27.7% per year, see calculation for X below), and the 3.5<sup>th</sup> root was calculated for the yearly probability during the next 3.5 years (13% per year, see calculation for Y below).

$$X^{1.5} = (1-0.385)$$

$$X^{1.5} = 0.615$$

$$X = 0.723$$

$1 - X$  = Annual rate of metastatic spread during first 1.5 years following local recurrence

$$1 - X = 0.277 \text{ or } 27.7\%$$

$$Y^{3.5} = (1-0.385)$$

$$Y^{3.5} = 0.615$$

$$Y = 0.87$$

$1 - Y$  = Annual rate of metastatic spread during next 3.5 years

$$1 - Y = 0.13 \text{ or } 13\%$$

This assumes that the rate of metastatic spread following local recurrence is constant during the first 1.5 years following local recurrence (at 27% per year), and constant again during the next 3.5 years after the local recurrence (at 13% per year). A yearly rate of metastasis of 27% for 1.5 years followed by a yearly rate of metastasis of 13% for 3.5 years results in a 5 year metastatic rate following local recurrence of 77%, with half of the metastases occurring in the first 1.5 years and half in the next 3.5 years.

It is the difference between this salvage rate and the salvage rate of local recurrences detected by surveillance mammography that will be the most important parameter with respect to the cost-effectiveness of routine surveillance mammography in this population. It will be assumed that local recurrences detected by surveillance mammography will share one key characteristic in common with those detected by clinical examination in that local recurrences detected within the first 1.5 years will be more aggressive and more likely to metastasize than those which recur after this time period<sup>78</sup>. Different values of yearly probability of metastatic spread in women with local recurrence detected by surveillance mammography will be used in the model to determine the threshold at which routine surveillance mammography will be cost-effective.

#### 4.5 *Results*

Threshold values of relative risk reduction of metastatic spread following local recurrence detected by surveillance mammography of women with breast reconstruction were determined with the following parameters as described in the methods section:

- 50% of local recurrences are detectable by surveillance mammography before they are clinically evident
- The false positive rate of surveillance mammography of reconstructed breasts is 1%
- Cost effectiveness threshold set at \$50 000 per LY Gained for the cost-effectiveness analysis, or
- \$50 000 per QALY for the cost-utility analysis

The minimum relative risk reduction required to reach the threshold value of \$50 000 per LY gained is 3.34%. The minimum relative risk reduction required to be reach the threshold

value of \$50 000 per QALY gained is 2.34%. The incremental cost effectiveness at various relative risks can be seen in Figure 3.

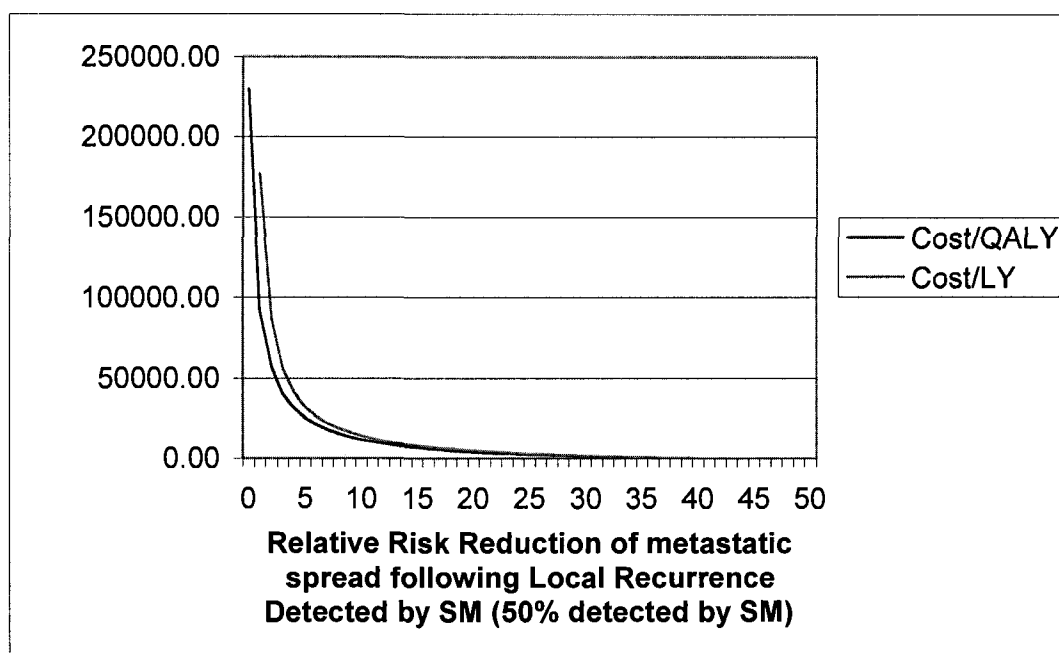


Figure 3 – Incremental cost per QALY and per life year (LY) by relative risk reduction of metastatic spread following local recurrence detected by surveillance mammography (SM) (50% of local recurrences detected by SM in model). Threshold values are 3.34% for Cost/LY and 2.34% for Cost/QALY

#### 4.5.1 Sensitivity Analysis

The first parameter evaluated in the sensitivity analysis was the sensitivity of surveillance mammography in breast reconstruction. To evaluate this, the proportion of local recurrences detected by surveillance mammography was altered. Proportions tested in this analysis were 25% and 75%. This analysis using cost per LY can be seen in Figure 4, and using cost per QALY can be seen in Figure 5. The remainder of the sensitivity analysis consisted of

altering values for annual rate of local recurrence, the false positive rate, and the costs of diagnosis, treatment and follow up of metastatic disease. These results can be seen in Table X. These sensitivity analyses found the model to be most sensitive to the rate of false positive surveillance mammograms. Manipulating the cost of metastatic diagnosis, metastatic treatment and metastatic follow up resulted in only minimal changes to the relative risk reduction required for achieving threshold cost effectiveness. Wide manipulation of the weights of women diagnosed with local recurrence undergoing radiation, surgery, or chemotherapy resulted in no change to the threshold risk reduction. This can be explained by the fact that surveillance mammography does not impact the number of women who will require treatment for local recurrence, it may simply detect them earlier.

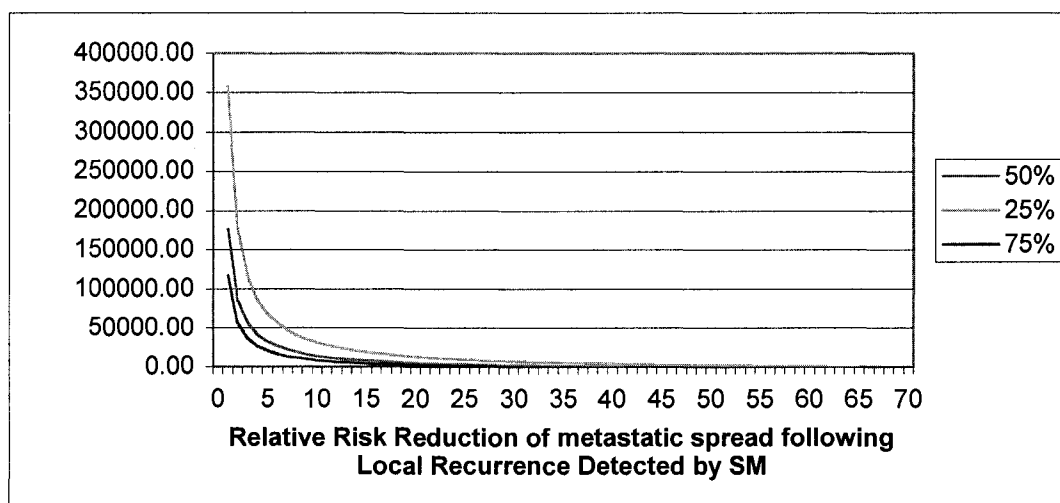


Figure 4 – Incremental cost per life year (LY) at different sensitivities of surveillance mammography (SM). The threshold values are relative risk reductions of 6.5% when 25% of local recurrences are detected by SM and 2.5% when 75% of local recurrences are detected by SM



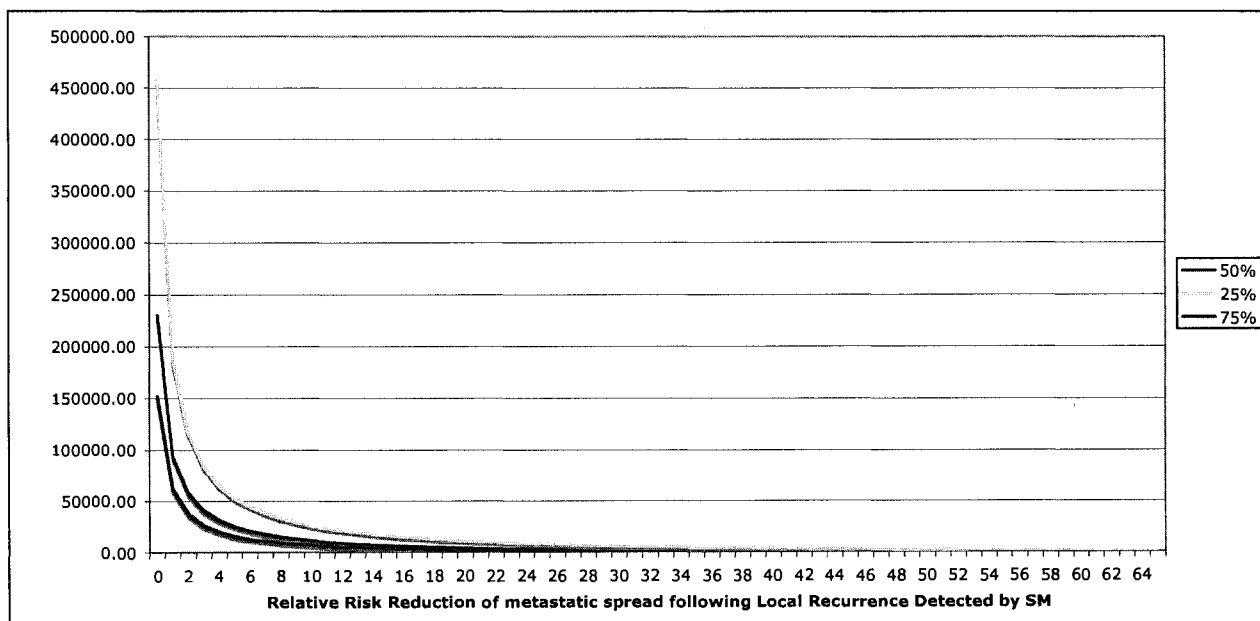


Figure 5 – Incremental cost per quality adjusted life year (QALY) at different sensitivities of surveillance mammography (SM). The threshold values are relative risk reductions of 5.5% when 25% of local recurrences are detected by SM and 1.5% when 75% of local recurrences are detected by SM

Table X – Sensitivity analysis. Results demonstrate the relative risk reductions required for cost-effectiveness at different settings of each variable in the model

| Variable                            | Original Estimate | Manipulation | Threshold RR (LY) | Threshold RR (QALY) |
|-------------------------------------|-------------------|--------------|-------------------|---------------------|
| <b>False Positive Rate</b>          | 1%                |              | 3.34              | 2.34                |
|                                     |                   | X 5 (5%)     | 4.86              | 3.71                |
|                                     |                   | X 10 (10%)   | 6.72              | 5.38                |
| <b>Cost of Metastatic Diagnosis</b> | 2160.10           |              | 3.34              | 2.34                |
|                                     |                   | + 50%        | 3.34              | 2.34                |
|                                     |                   | + 25%        | 3.34              | 2.34                |
|                                     |                   | - 25%        | 3.35              | 2.34                |
|                                     |                   | - 50%        | 3.35              | 2.35                |
| <b>Cost of Metastatic Treatment</b> | 8071.45           |              | 3.34              | 2.34                |
|                                     |                   | + 50%        | 3.32              | 2.32                |
|                                     |                   | + 25%        | 3.33              | 2.33                |
|                                     |                   | - 25%        | 3.36              | 2.35                |
|                                     |                   | - 50%        | 3.37              | 2.36                |
| <b>Cost of Metastatic Follow up</b> | 1864.09           |              | 3.34              | 2.34                |
|                                     |                   | + 50%        | 3.26              | 2.29                |
|                                     |                   | + 25%        | 3.3               | 2.32                |
|                                     |                   | - 25%        | 3.39              | 2.37                |
|                                     |                   | - 50%        | 3.43              | 2.39                |
| <b>Rate of Local Recurrence</b>     | 1% per year       |              | 3.34              | 2.34                |
|                                     |                   | +50%         | 2.24              | 1.36                |
|                                     |                   | +25%         | 2.68              | 1.75                |
|                                     |                   | -25%         | 4.44              | 3.32                |
|                                     |                   | -50%         | 6.58              | 5.24                |

#### 4.6 Discussion

Analysis was conducted to determine the threshold value for reduction of metastatic risk following the diagnosis of local recurrence by surveillance mammography in a reconstructed breast versus a local recurrence detected by clinical examination whereby surveillance mammography of the reconstructed breast could be deemed cost effective. The findings suggest that surveillance mammography of a reconstructed breast becomes cost effective (\$50 000 per LY gained) with a relative risk reduction of metastatic disease of 3.34%. This signifies that 3.34% of events (metastasis following local recurrence) need to be prevented in order to be cost effective. In the secondary cost utility analysis, the threshold is lower: a relative risk reduction of 2.34% is required for cost-effectiveness to be achieved. This difference is explained to some extent by the fact that the sample from which the utility weights were derived felt that some comfort would be found in the knowledge that a local recurrence was detected by surveillance mammography prior to it becoming clinically evident, potentially improving the likelihood of achieving local control. If one out of 30 women (3.34% of women =  $1:1/0.034 = 1:29.9$ ) with local recurrence detected by surveillance mammography that would otherwise have gone on to have metastatic spread is prevented from developing metastatic disease, the surveillance mammography program would be cost effective. If the cost utility analysis is used, this becomes 1 out of 42 (threshold relative risk reduction of 2.34%; 2.34% of women =  $1:1/0.0234 = 1:42.7$ ) women.

Local recurrences detected by surveillance mammography among women without breast reconstruction have been shown to be at a lower stage than those detected clinically<sup>20</sup>. As locally recurrent breast cancer detected by surveillance mammography among women with breast reconstruction who participate in such a surveillance program would be inherently different from those that are diagnosed by clinical examination, it is reasonable to

expect that they too would be at a lower stage. Although there is no clinical evidence guiding the likelihood of salvage following local recurrence detected by surveillance mammography in women with breast reconstruction, the threshold values derived from this economic analysis do not seem to be unreasonable.

When the results of the model are evaluated through sensitivity analysis, it was found that the results were most sensitive to the rate of false positive examinations and the proportion of recurrences detected by surveillance mammography. Even with an extreme false positive rate of 10%, the risk reduction at which the program would be cost effective is only 6.72%. Altering the annual rate of local recurrence between 0.5% and 1.5%, the threshold relative risk reduction increased only to 6.58%. When the sensitivity of surveillance mammography was manipulated such that only 25% of local recurrences were detected by surveillance mammography, it was found that the threshold was a risk reduction of only 6.5%. Altering the costs of various health states, including diagnostic and treatment costs, by 50% above and below the estimate did not alter the threshold by more than 0.09%. This indicates that the findings of this economic analysis are relatively insensitive to uncertainty in the other variables, and withstand even significant uncertainty in cost.

#### *4.7 Conclusion*

In the absence of clinical evidence to guide the clinician with regards to surveillance mammography of women with breast reconstruction, it is important to evaluate the economic impact that such a program would have. If, to be cost effective, surveillance mammography of reconstructed breasts required a drastic change in the rate of salvage following diagnosis of local recurrence it would not be advisable to recommend such a surveillance program in the absence of clinical evidence. The findings of this economic analysis, however, suggest

that the recommendation would be cost effective if only a very small proportion of women with local recurrence are prevented from developing metastatic spread. Furthermore, the cost effectiveness of the practice increases significantly as the salvage rate increases.

Based on this economic analysis, it can be suggested that only a small proportion of women with local recurrence in their reconstructed breast would need to be prevented from developing metastatic spread by early detection through surveillance mammography for cost effectiveness to be achieved. This analysis does not support further conclusions regarding the effectiveness or safety of surveillance mammography of the reconstructed breast. No clinical recommendations can be made regarding surveillance mammography of the reconstructed breast based solely upon the data and results presented in this economic analysis. Further study is required to provide the evidence needed to support the assumptions made in this analysis in order to provide a definitive conclusion.

## 5.0 Chapter 5 – Summary and Conclusions

The American Society of Clinical Oncology and the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer recommend regular surveillance mammograms for all women with a prior diagnosis of breast cancer<sup>6,21</sup>. In these recommendations, however, there is no mention of women who have undergone breast reconstruction following mastectomy<sup>4-11</sup>. An attempt was made in this thesis to address this void. A multi-method approach was used: (1) a systematic review of existing literature, (2) a population based cohort study of women with a diagnosis of breast cancer; and (3) an economic analysis of a surveillance program consisting of yearly mammography of the reconstructed breast.

As stated in section 1.3.5, the specific objectives of this thesis were:

1. To conduct a systematic review of the literature related to surveillance mammography of women who have undergone breast reconstruction following mastectomy.
2. To use data from an existing Ontario cohort to evaluate the detection of local breast cancer recurrence by surveillance mammography in women who have undergone breast reconstruction following mastectomy.
3. To use data from an existing Ontario cohort to evaluate the rate of false positive and false negative surveillance mammograms in women who have undergone breast reconstruction following mastectomy.
4. To compare the rates of both false positive and false negative surveillance mammograms in women who have undergone breast reconstruction following mastectomy (derived

from objective 3) to screening mammograms in the general population (derived from the literature).

5. To perform an economic evaluation of surveillance mammography in women who have undergone breast reconstruction following mastectomy.

As stated in section 1.3.6, the hypotheses to be tested in this thesis were:

1. Surveillance mammography detects local recurrence in the reconstructed breast earlier than clinical examination and diagnostic mammography in women who have undergone breast reconstruction following mastectomy.
2. False positives are more common in surveillance mammograms than in diagnostic mammograms in women who have undergone breast reconstruction following mastectomy.
3. False negatives are more common in surveillance mammograms than in diagnostic mammograms in women who have undergone breast reconstruction following mastectomy.
4. Surveillance mammography of the reconstructed breast in women who have undergone breast reconstruction following mastectomy is cost effective.

These objectives and hypotheses will be discussed in the following sections.

### *5.1 Systematic Review*

To address the first objective of the thesis, a systematic review of the literature related to surveillance mammography of women who have undergone breast reconstruction following mastectomy was performed. This systematic review identified a paucity of clinical evidence

addressing the issue of surveillance mammography for women who have undergone breast reconstruction following mastectomy. Only case reports and case series are available to guide the clinician in deciding whether or not to recommend surveillance mammography of the ipsilateral breast of women with breast reconstruction. However, the review did identify several papers documenting local recurrences in reconstructed breasts, and that some of these can be detected by surveillance mammography. A number of the papers questioned the economic value of such a practice, but none conducted an economic analysis. The strongest study addressing this issue lacked generalizability as it selected only patients treated and followed at a single institution who underwent surveillance mammography at their treating physician's discretion<sup>39</sup>.

## *5.2 Cohort Study*

This cohort study was the first attempt to use a population based cohort to evaluate surveillance mammography of the ipsilateral breast of women with breast reconstruction. Survival would be the best outcome to evaluate in a study addressing surveillance mammography, as survival may improve from its use. With only ten years of follow up for the cohort, however, a surrogate outcome was chosen. The outcome of interest was stage of local recurrence detected by surveillance mammography versus those detected by clinical examination. However, in the cohort no local recurrences were detected by surveillance mammography, and no false positive mammograms were reported among the surveillance or diagnostic mammograms of reconstructed breasts. The objectives of the cohort study were to evaluate the detection of local recurrence by surveillance mammography among women with breast reconstruction, to evaluate the rates of false positive and false negative surveillance mammograms among women with breast reconstruction, and to compare these rates to those



of screening mammography among the general population of women. With the lack of locally recurrent breast cancer among the patients in the cohort, the proposed analysis was not performed. As such, objectives 2, 3 and 4 could not be achieved, and hypotheses 1, 2 and 3 were not tested, as the results of the tests would have been of minimal value given the lack of data.

It has previously been suggested that surveillance mammography would be of more use to women reconstructed with an implant<sup>41</sup>. This was not seen to affect the use of surveillance mammography in the cohort, as mammograms were used for women reconstructed both with and without implants. Thus it appears that clinicians are not more or less likely to obtain surveillance mammograms based on the type of reconstruction.

Perhaps the most interesting finding from the study is that 39% of women had at least one mammogram of their reconstructed breast. This clearly shows that there is uncertainty surrounding the use of this investigation, and points to the need for better studies and guidelines to instruct the clinician on the use of mammography of the reconstructed breast.

Population based cohort studies have advantages and disadvantages. The major advantages of population based cohort studies include generalizability and capture. As population based cohorts include all members of the population with a particular attribute, in this case a diagnosis of breast cancer, they are very generalizable and have a high degree of external validity. External validity has been defined as “the degree to which the results of a study are relevant for populations other than the target population”<sup>98</sup>. The largest previous study evaluating the issue of surveillance mammography for women with breast reconstruction lacked both capture and generalizability as it included only patients treated and followed at a single institution<sup>39</sup>.

One disadvantage of population based cohorts has to do with data collection. These cohorts rely on patients treated at a number of locations and data that are collected routinely rather than specific to the study objectives. Hence, data capture might not be complete and data elements might have different operational definitions. This may explain the fact that only 69% of the cohort had any information regarding mammography.

The major disadvantage of population based cohort studies has to do with sample size. When studying an uncommon condition within the population, population based studies require very large numbers to collect a sample large enough for meaningful analysis. This problem was encountered in the cohort study component of this thesis. Even with 1526 women with a diagnosis of breast cancer in the enriched cohort used in the analysis, only 55 women in the cohort had undergone mastectomy and breast reconstruction. Although this number was too low to draw conclusions based on statistical analysis, it represents the only attempt at a population based cohort study in the literature. In order to have a sample large enough to detect a 10% decrease in metastatic spread (77% risk of metastasis after local recurrence<sup>78</sup> to 69.3%,  $\alpha = 0.05$ ,  $\beta = 0.20$ ) with the use of surveillance mammography among women with breast reconstruction, there would need to be 1036 women in the cohort with local recurrence of breast cancer following mastectomy and breast reconstruction (sample size calculation made with Epicalc 2000). In order to achieve this with a population based cohort having the characteristics of the one used in this study, there would need to be 527 000 women with a diagnosis of breast cancer in the cohort. Although this concern regarding the sample size was identified before the study was performed, it was expected that the sample size was enough to provide the best available data for inputting into the economic model.

This sample size problem indicates that a population based cohort is not a feasible study design to measure the survival benefit of surveillance mammography following breast reconstruction. It did, however, provide useful information regarding the current variation in the patterns of practice of surveillance mammography among women with breast reconstruction.

### *5.3 Economic Analysis*

The final objective of the thesis was to perform an economic evaluation of surveillance mammography for women who have undergone breast reconstruction following mastectomy. This objective was met by performing an economic evaluation employing a Markov model to identify the proportion of local recurrences detected by surveillance mammography needed to be cost effective. The hypothesis stated that surveillance mammography of the reconstructed breast in women who have undergone breast reconstruction following mastectomy is cost effective. The trade off that determines cost effectiveness is the added cost of bilateral surveillance mammography and false positive exams versus the potential reduction in metastatic spread for local recurrences detected by surveillance mammography. A Markov model allows for transition over time between the multiple possible health states involved in breast cancer. Although it was planned to use data from the cohort for the population of transition probabilities in the model, these data were insufficient. As such, the majority of the transition probabilities were obtained from the literature.

The base cost effectiveness analysis found that in order to be cost effective, there must be at least a 3.34% reduction in the risk of metastasis following a local recurrence detected by surveillance mammography. Sensitivity testing demonstrated these relative risk reduction required for cost effectiveness to be similar when the variables were manipulated.

The relative risk reduction required for cost effectiveness was found to be most dependent on the proportion of local recurrences detected by surveillance mammography and the rate of false positive examinations. In the parameters set by this model, minimal prevention of metastatic spread is required for bilateral surveillance mammography for women with breast reconstruction to be cost effective at a threshold of \$50 000 per life year gained. Given the exploratory nature of the analysis, as well as the number of assumptions, the hypothesis that surveillance mammography of the reconstructed breast in women who have undergone breast reconstruction following mastectomy is cost effective could not be supported by this study.

#### *5.4 Conclusion*

In a recent editorial in the Journal of the National Cancer Institute, Whelan and Levine state that with more than 1 000 000 women per year being affected by breast cancer worldwide, treatment policies directed at small subgroups are likely to affect thousands of women per year<sup>99</sup>. Although breast reconstruction is an uncommon event in the cohort, the issue of surveillance mammography for these women remains a common concern for the many clinicians involved in their care. Although BCS is an appropriate treatment and its use is increasing, mastectomy remains a common treatment for women with breast cancer. As women with breast cancer are living longer, and the proportion of women with mastectomy who pursue breast reconstruction is increasing,<sup>29-32</sup> the follow up of these patients is an important issue for their oncologist, family physician, ablative surgeon and reconstructive surgeon. The clinicians following these women after their cancer treatment are currently making decisions on surveillance without any evidence or recommendations to guide them.

The systematic review identified several studies that have documented women who have been diagnosed with local recurrence by surveillance mammography within their

reconstructed breast. The finding from the cohort study that only 39% of women underwent surveillance mammography of their reconstructed breast demonstrates that clinical uncertainty exists. In the economic analysis, it was shown that only a minimal decrease in metastatic risk would be required for the adoption of a surveillance practice to be economically sound.

The findings from this thesis point to two clinical recommendations until clinical evidence becomes available. First, based on the presence of residual breast tissue in mastectomy sites, the ability of surveillance mammography to detect local recurrence and the low salvage rate of locally recurrent disease required for cost effectiveness, it is prudent to recommend that women with breast reconstruction undergo yearly surveillance mammography of their reconstructed breast, as well as their contralateral breast as previously recommended. Second, as breast reconstruction becomes more common, further more definitive research is needed to show a survival benefit from the use of surveillance mammography among these women. Given that false negative surveillance mammograms were found in the cohort study, future research should also include an evaluation of other imaging modalities, such as MRI, in this clinical situation.

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**Appendix A – OHIP Codes for Mastectomy and Breast Reconstruction****Mastectomy**Code   Description

R108   Simple Mastectomy

R117   Subcutaneous mastectomy with nipple preservation

R109   Mastectomy, radical or modified radical (with or without biopsy)

**Breast Reconstruction**Code   Description

R119   Breast mound creation by prosthesis and/or soft tissue

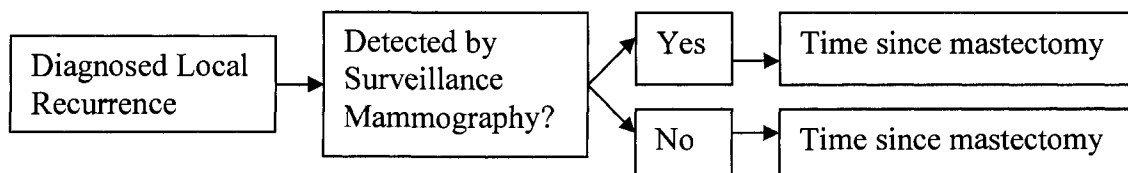
R118   Breast skin reconstruction by local flaps or grafts

R006   Myocutaneous Flaps - Pectoralis major, latissimus dorsi, unilateral rectus abdominus

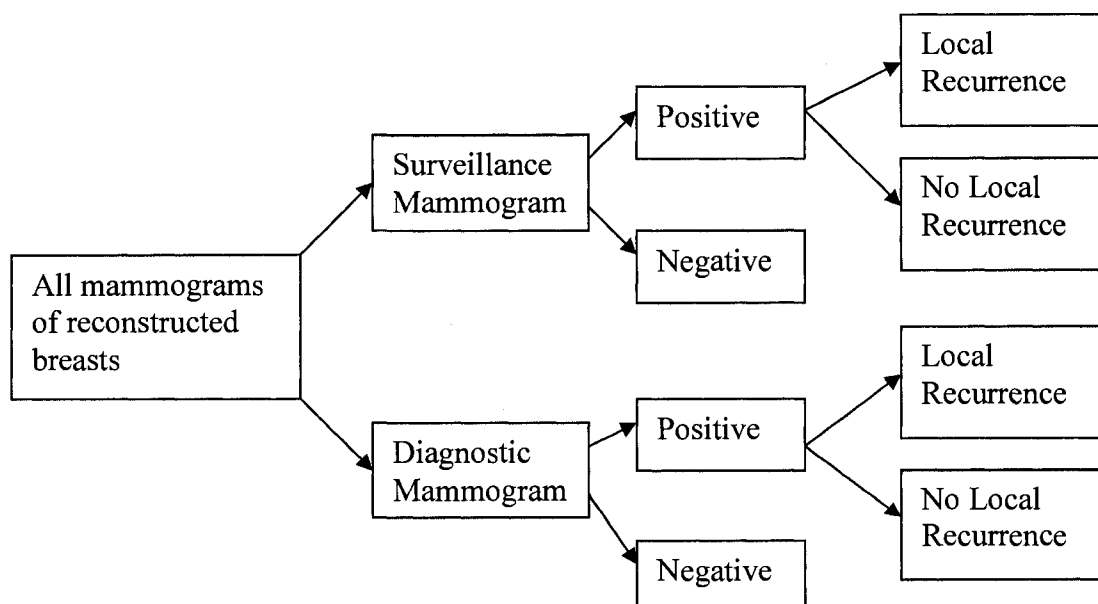
R008   Lower transverse rectus abdominus myocutaneous flap

## Appendix B – Schematic Representation of Cohort Analysis

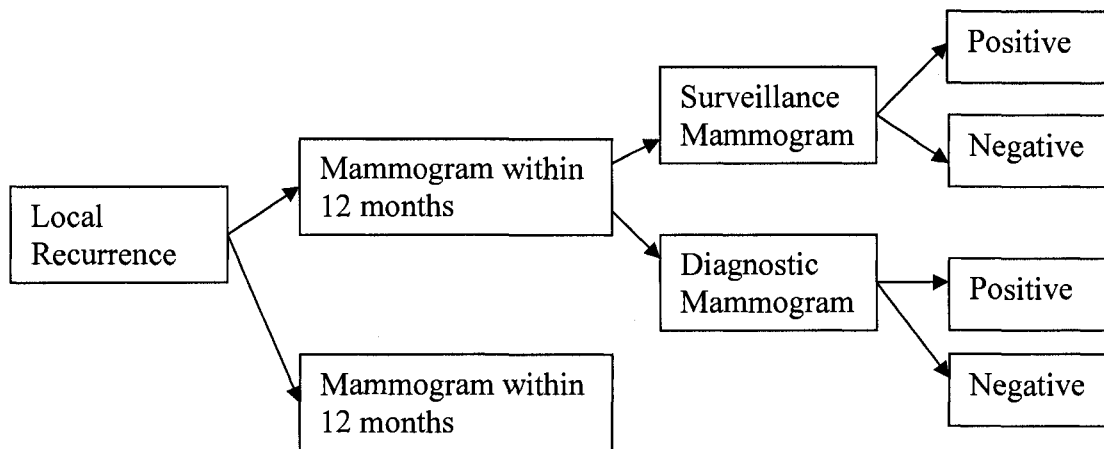
**Hypothesis 1.** Surveillance mammography detects local recurrence earlier than clinical examination and diagnostic mammography of the reconstructed breast in women with breast reconstruction following mastectomy for breast cancer.



**Hypothesis 2.** False positives are more common in surveillance mammograms of reconstructed breasts than in diagnostic mammograms among women with breast reconstruction following mastectomy for breast cancer.



**Hypothesis 3.** False negatives are more common in surveillance mammograms of reconstructed breasts than in diagnostic mammograms among women with breast reconstruction following mastectomy for breast cancer.



## Appendix C

### Visual Analog Scale

