Explaining Variation in Clinical Practice: Surgical Treatment of Early Stage Breast Cancer

by

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ABSTRACT

Background: Breast conserving surgery (BCS) followed by radiation is the preferred treatment option for early stage breast cancer because it is less invasive than the alternative treatment, mastectomy, and provides a better cosmetic outcome and a superior quality of life. Positive surgical margins after breast conserving surgery (BCS), however, necessitate re-excision surgery by further BCS or by mastectomy. Re-excision is associated with greater morbidity, patient anxiety, poor cosmetic outcome, delayed initiation of adjuvant therapies, and increased medical cost.

Objectives: The primary objectives of this research were to: 1) investigate the relationships between clinical, patient, provider and geographic factors and surgery type received; 2) investigate the relationships between clinical, patient, provider and geographic factors and receipt of re-excision surgery; 3) quantify residual surgeon and hospital-specific variation associated with surgery type received and receipt of re-excision and; 4) investigate if re-excision is associated with all cause and breast cancer-specific mortality among patients who receive re-excision, compared to those who receive BCS without re-excision and those who receive an initial mastectomy.

Methods: All women diagnosed with stage I-III breast cancer in Alberta from 2002 to 2010 were identified from the Alberta Cancer Registry; demographic, clinical and treatment information was obtained from this source. Alberta Health Physician Claims data were used to identify the type of first breast cancer surgery after diagnosis, subsequent re-excisions within 1 year of initial surgery, and anonymized physician identifiers associated with each procedure. Multilevel logistic regression with surgeons and hospitals as crossed random effects were used to estimate the adjusted odds ratios of mastectomy and of re-excision by the factors of interest. Poisson regression models were fitted to compare all-cause and breast cancer-specific mortality by surgery pattern.

Results: Mastectomy was received by 51% of patients and was found to be inversely related to surgeon volume among stage I and II patients. Odds ratios of mastectomy varied widely by individual surgeon and by hospital beyond the variation explained by the factors investigated. Re-excision surgery was received by 19% of patients who initially received BCS. Increasing patient age was associated with re-excision and the odds of re-excision varied significantly through the province. BCS followed by re-excision was not associated with greater all-cause or breast cancer-specific mortality compared to than those who received BCS without re-excision.

Conclusions: Both clinical and health system factors are associated with mastectomy and re-excision among breast cancer patients in Alberta. The significant surgeon-specific variation in the likelihood of BCS, and the geographic and surgeon-specific variation of re-excision is concerning. Further research is necessary to understand the reasons for the observed variation so appropriate interventions can be developed and applied.

PREFACE

This thesis is an original work by Stacey Fisher with supervision from Dr. Yutaka Yasui and Dr. Marcy Winget. The larger research project, of which this thesis is part, received research ethics approval from the University of Alberta Research Ethics Board, Project name "Population-based evaluation of quality and timeliness of breast cancer care", No. Proo00018912, April 16, 2012.

Chapter 2 of this thesis will be submitted as Fisher S, Yasui Y, Dabbs K, Winget M. Using multi-level models to explain variation in clinical practice: Surgeon volume and the surgical treatment of breast cancer. Chapter 3 of this thesis will be submitted as Fisher S, Yasui Y, Dabbs K, Winget M. Re-excision following breast conserving surgery and survival in early stage breast cancer patients: A population-based study. I was involved in the design of the studies and was responsible for the analysis and interpretation of the data, as well as the drafting and revising of the manuscripts. Dr. Kelly Dabbs was involved in the design of the studies, interpretation of the data, and revision of the manuscripts. Dr. Yutaka Yasui and Dr. Marcy Winget were involved in the conception and design of the studies, analysis and interpretation of the data, and revision of the manuscripts.

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BCS	Breast conserving surgery
CI	Confidence interval
ICD-O-3	International Classification of Diseases for Oncology 3rd edition
OR	Odds ratio
SCV	Systematic component of variation
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program

CHAPTER 1: INTRODUCTION

1.1 OVERVIEW

This thesis research focuses on the investigation of clinical practice variation, specifically variation in the surgical treatment of early stage breast cancer in Alberta, Canada. The primary outcomes examined are initial surgical procedure type and receipt of re-excision surgery. A brief examination of the survival of patients who receive re-excision surgery compared to those who do not is also performed.

The following literature review begins by broadly discussing health care variation and its investigation, and the importance of variation research. Next, options for the surgical treatment of early stage breast cancer are summarized and the clinical, patient, provider and geographic factors that have been associated with initial surgical procedure type and receipt of re-excision surgery are reviewed to provide context for the rest of the thesis. This literature review ends with a summary and discussion of the specific motivation behind this research.

1.2 VARIATION IN CLINICAL PRACTICE

1.2.1 Overview

Significant variation in clinical practice has been widely documented even for common, clinically effective procedures [1-5]. For example, patients residing in remote and rural regions tend to have a lower uptake of screening services[6-8], are less likely to receive care concordant with clinical guidelines[9-11], and have poorer access to appropriate end of life services[12-14] compared to patients residing in urban regions. Also, patients of surgeons with high caseload volumes have been found to have reduced surgical complications and shorter durations of hospital stay, in addition to reduced mortality, compared to patients of low volume surgeons[15-19]. The investigation and mitigation of health care variation such as these is critical, as it has the potential to improve health care access and efficiency, and the overall health of the population.

It is generally accepted that practice variation associated with geographic patterns of illness and certain case-mix characteristics is acceptable (warranted), and that practice variation that has a negative impact on care should be eliminated (unwarranted). It is very difficult, however, to determine what proportion of observed variation is unwarranted, and to what factors it can be attributed. Several frameworks have been developed to help with this[20-24], which include definitions of unwarranted variation such as, variation that 'cannot be explained on the basis of illness, patients' preferences, or dictates of scientific medicine'[20] and 'that is explained not by population differences but by the quality, appropriateness, and efficiency of health care'[23]. As has been discussed by Mercui *et al.*[25], however, the practical use of these definitions to identify sources of unwarranted variation is difficult. For example, sufficient information to adequately measure sources of warranted and unwarranted variation is often not available, and measurement of factors such as patient preferences is challenging. It is also not clear what role context plays in determining if variation associated with a particular factor is unwarranted[25].

Despite these challenges, important research on sources of clinical care variation has been performed in a variety of clinical and geographical contexts. Wennberg was one of the first to describe unwarranted variation after finding that variation in patient case-mix and care demand was often not able to fully explain observed heterogeneity of health service utilization[25, 26]. He hypothesized this variation to be associated with physician practice style[26]. Clinical variation has since been associated with many physician-specific factors including age[27, 28], specialty[29, 30], years in practice[30, 31], location of medical school training[27, 31], interpretational differences of clinical findings[32], tolerance of specific risks[33], fear of malpractice[28, 34], and the extent to which physicians incorporate patient preferences[1,4]. Contextual and environmental factors have also been found to greatly influence physician practice; characteristics of the training environment[27, 28, 35], including organizational setting[25, 27, 28], and available resources[25, 36] have been significantly associated with clinical heterogeneity.

The Canadian federal government has called for increased measurement and reporting of health care system delivery and performance to aid in the understanding of clinical variation and the identification of sources of unwarranted variation[37, 38]. Understanding treatment patterns is useful for informing policies and strategies for minimizing unwarranted practice variation while maximizing care quality. Hopefully these efforts will result in quality improvement of the services provided by Canada's health care system.

1.2.2 Quantifying Clinical Variation

Measurement of clinical variation typically involves the use of large administrative databases to determine population-based rates of service utilization by a unit of interest, such as geographic region or health care provider. These rates can be compared in many ways, from simple comparisons of crude values to more complex analyses that adjust for sources of warranted variation. Simple comparisons using range or standard deviation can only provide information about the distribution of the outcome across the units of interest, including all variation by both warranted and unwarranted sources, and therefore are of limited use when attempting to identify sources of unwarranted variation[4]. The systematic component of variation (SCV), developed by McPherson *et al.*[39], is a commonly used statistic that can account for differing patient characteristics within the population. This statistic quantifies the variation between the units of interest by comparing the number of observed and expected outcomes, while accounting for warranted variation associated with, usually, age and gender.

Empirical Bayes is a less often used means of quantifying clinical variation[40]. It involves estimation of the rates associated with each unit, rather than testing the significance of the observed versus expected counts as is done with the SCV. Multi-level analyses with adjustment for factors associated with warranted variation and empirical Bayes estimation have the potential to provide information about sources of unwarranted variation specifically, which can then be targeted for intervention. Several studies[41, 42] have reported that Empirical Bayes analysis provides robust variation estimates compared to the SCV, and researchers have recommended an increase in the use of empirical Bayes techniques in variation studies[41].

1.2.3 Addressing Unwarranted Variation

Once sources of inappropriate variation have been identified, active efforts to reduce variation-associated disparities have the potential to improve care quality. Several means of addressing inappropriate variation in clinical practice have been identified[43, 44]; here we will discuss the use of clinical practice guidelines, patient decision aids, and performance indicators.

One means of minimizing practice variation while optimizing care quality is through the development and thorough implementation of clinical practice guidelines, which provide evidence-based clinical guidance to all physicians regarding the treatment of a specific disease or condition[43-45]. However, clinical practice guidelines have been reported to sometimes have very little impact on day-to-day clinical practice and are frequently ignored by many physicians[46]; even with the existence of well-established guidelines, the proportion of patients who receive guideline concordant treatment is often low[47-49]. Many reasons have been hypothesized for failures of clinical practice guidelines to influence physician practices including a lack of physician awareness, familiarity or agreement on the guidelines, or other external barriers such as a lack of institution support[46]. Some of these barriers can be mitigated by a local focus on their implementation, as physician awareness and familiarity with the guidelines can be prioritized and likely achieved more easily within a smaller group of providers[50].

When more than one reasonable treatment option is available, patient preference is considered to be vitally important to clinical decision-making, as individual patients may make very different value judgments about issues such as immediate versus delayed risks of mortality and quality of life[1, 51]. However, the preferences of individual physicians, as opposed to the preferences of the patient, have been found to be strongly associated with the treatment received[52]. Meta-analysis has demonstrated that shared-decision making supported by the use of patient decision aids help to improve patient knowledge, promote a more accurate perception of risks and benefits, and result in care more aligned with patient values[53]. Education of physicians regarding the importance of shared-decision making and the use of patient decision aids therefore has the potential to reduce treatment variation associated with preference-sensitive care by increasing warranted variation associated with patient preference[1, 43, 54].

Another means of minimizing practice variation is through the use of performance indicators. Feedback on the relative performance of physicians compared to their peers or to established performance indicators has been found to lead to measurable improvements in patient care[55, 56]. The Canadian federal government has prioritized the establishment of performance indicators to measure and compare the quality of health services delivered across the country[37].

1.3 PRIMARY SURGICAL TREATMENT FOR EARLY STAGE BREAST CANCER

1.3.1 Overview

Among Canadian females, breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death[57]. A multimodal approach to treatment is typically utilized for patients with stage I, II and III breast cancer, which may include surgical treatment, radiotherapy, chemotherapy and/or hormone therapy.

Surgical treatment typically involves either breast conserving surgery (BCS) or mastectomy. BCS involves the removal of the tumour in addition to a small margin of surrounding tissue, while mastectomy involves the removal of the entire breast that has cancer. These options are the result of six randomized trials, some with more than 20 years of follow-up, which have demonstrated equivalent survival outcomes for patients who receive BCS followed by radiotherapy, and mastectomy[58-63]. BCS followed by radiotherapy is generally the preferred treatment option as BCS is less invasive, associated with less morbidity and a better cosmetic outcome than mastectomy[64]. Research also suggests that patients who receive BCS have significantly superior body image and sexual functioning, and a higher surgical satisfaction rate compared to those who receive mastectomy[65-69].

The proportion of invasive breast cancer patients who received BCS in Canada from 2007 to 2010 has been estimated to be 61%[70]. This is similar to that found in the United States where BCS rates range from 50-70%[71-75], while in the Netherlands estimates are closer to 50% of patients[76].

1.3.2 Clinical Considerations

There are many clinical contraindications for breast conserving surgery. Patients with multicentric cancer (tumors in more than one quadrant of the breast), significant diffuse calcifications, or a small breast-to-tumor ratio are generally advised to receive mastectomy as it is difficult to obtain an acceptable cosmetic outcome with BCS while minimizing the risk of recurrence[77, 78]. Patients with a family history of breast cancer or BRCA1/2 mutations are also typically advised to receive mastectomy, as the risk of recurrence and a second primary cancer following BCS is high for these women[77]. Some women with genetic predisposition to breast cancer chose to receive prophylactic bilateral mastectomy.

Since receipt of radiotherapy after breast conserving surgery is necessary to achieve survival equivalent to mastectomy, women who are not able to receive radiotherapy are also generally advised to receive mastectomy. This includes patients who have received significant prior radiotherapy to the chest wall and patients who are pregnant, unless it is perceived to be safe to wait until after delivery for adjuvant therapy. Patients with certain comorbid conditions such as connective tissue disorders often receive mastectomy as they tend to be less able to tolerate radiotherapy and are more likely to experience significant complications[79, 80].

1.3.3 Patient Characteristics and Preferences

Patient age is a significant predictor of surgical treatment received by women with early stage breast cancer. Receipt of mastectomy is generally highest among the youngest and the oldest patients, while women 50-69 years are more likely to receive BCS[81-84]. It is thought that older women tend to receive mastectomy more than middle-age women because they are more likely to have significant comorbidities, are more likely to depend on others for transportation, are less concerned about body image, and are more inclined to avoid radiotherapy[70, 85, 86]. Young women may chose mastectomy because of increased fear of recurrence due to a long life expectancy, and because cancer diagnosed in young women tends to be more aggressive than that found in older women[87, 88], causing patients and their physicians to favour more aggressive treatment.

Since clinical trials indicate that BCS with radiotherapy and mastectomy are associated with equivalent survival, patient preference plays a key role in determining the best surgical option for an individual breast cancer patient. This has become increasingly important as emphasis of shared decision-making and patient autonomy has grown in health care. A systematic review of patient preferences among early stage breast cancer patients found that the most important factors that affect patient surgery preference was body image among those who chose BCS and survival/recurrence among those who preferred mastectomy[89]. Fear of recurrence is a very strong motivator to receive mastectomy for many women[90-92]. Interestingly, patients who are more involved in the decision making process of surgery type tend to receive mastectomy[93]. However, Katz *et al.*[94] found that less than 50% of women who received mastectomy correctly answered a question about the lack of a survival benefit with BCS and radiotherapy compared to mastectomy. Patient values, risk perceptions and knowledge are associated with surgical options received.

Socioeconomic status has also been significantly associated with type of surgical treatment received by early stage breast cancer patients, as women of low socioeconomic status tend to receive mastectomy[85, 86, 95-98]. This may be related to barriers to care such as difficultly committing to time-consuming radiotherapy treatment due to problems coordinating childcare, work schedules and access to transportation[86, 98, 99].

1.3.4 Provider Characteristics

The care received by breast cancer patients with similar clinical and demographic characteristics has been found to differ depending on characteristics of the clinical provider. Surgery type has been significantly associated with surgeon gender, training, and year of graduation[97, 100]. Surgeon and hospital volume have also been repeatedly associated with greater use of BCS[97, 98, 101-103], and patients who receive surgery in teaching hospitals are more likely to undergo BCS compared to those treated in non-teaching hospitals[104-106]. Provider's personal preferences also has an impact on the type of breast cancer surgery their patients tend to receive, as patient perceptions about what the surgeon thinks is best is strongly associated with their treatment preference[92, 94, 107].

1.3.5 Geographic Variation

Significant regional variation in surgical treatment for breast cancer has been reported across Canada[70, 108], as well as within Alberta[84]. An estimated 26% of invasive breast cancer patients in Quebec received mastectomy as opposed to BCS from 2007 to 2010, while 69% and 65% of patients in Newfoundland and Saskatchewan received mastectomy, respectively[70]. Significant geographic variation internationally has also been reported[105, 109, 110]. In the United Kingdom, mastectomy rates were found to vary from 25 to 45% between breast screening units, persisting after adjustment for patient case-mix[110].

Poor access to radiation therapy may be partly responsible for some of the observed geographic variation[111-113]. Boscoe *et al.*[111] reported that women in the United States who have to travel over 75 km to a radiotherapy center for treatment are 1.4 times more likely to receive a mastectomy compared to those have to travel less than 15 km. However, investigation of distance to radiation in some settings, including in Alberta[84], suggests that this is not always the case and may be instead related to provider-related factors[76, 109]. Availability of immediate breast reconstruction also affects mastectomy rates as use of breast reconstruction in Canada has been associated with residence in high income neighborhoods, among non-immigrant patients, treatment at a teaching hospital or a hospital with 2 or more plastic surgeons, and among patients who travel further to receive surgery[114].

1.4 RE-EXCISION FOLLOWING INITIAL BREAST CONSERVING SURGERY

1.4.1 Overview

In addition to an increased risk of recurrence, another disadvantage of receiving initial BCS as opposed to mastectomy is the risk of positive resection margins that may necessitate additional re-excision surgery by either further BCS or by mastectomy if there is little remaining breast tissue. The risk of local recurrence with positive surgical margins after initial BCS is 2-3 times greater than with negative margins[115]. Re-excision is associated with greater morbidity, patient anxiety, poorer cosmetic outcome, delayed initiation of adjuvant therapies, and increased medical cost[116-120].

After initial BCS, the outermost edges of the excised tissue are labelled with ink and the margin, the distance between the tumor and the edge of the excised tissue, is tested for the presence of cancer cells. Positive margins indicate that cancer cells are present on the outer edge of the tissue (touching ink), while negative margins indicate no cancerous cells are present on this edge[121]. Close margins indicate that cancer cells are found between the outer edge of the tissue and the distance classified as negative, the definition of which is not standardized. Recently, however, the Society of Surgical Oncology and the American Society of Radiation Oncology released a consensus guideline on this topic, concluding that margins wider than 'no ink on tumor' do not further reduce the risk of breast cancer recurrence for patients with stage I and II breast cancers[122].

Population-based estimates of re-excision rates among patients with invasive cancers range from 17% in Ireland to 23% in Canada[19, 123, 124, 125].

1.4.2 Clinical Considerations

As discussed above, the strongest predictor of re-excision following BCS is surgical margin status, as patients with positive margins require re-excision to adequately reduce future risk of local recurrence, and patients with negative margins do not, as all cancer was removed[122]. Other clinical factors associated with re-excision include larger tumor size[116, 126-129], greater breast density[130, 131], multifocality[131, 132], lobular histology[116, 126], lymph node involvement[126, 128] and non-palpable lesions[132].

1.4.3 Patient Characteristics

Receipt of re-excision is inversely associated with patient age[127, 128, 132, 133]. This may be because younger women have denser breast tissue compared to older women, reducing the ability of mammography to determine the extent of the tumor[130]. Young women may also place a greater value on a satisfactory cosmetic result compared to older patients, and therefore the initial excision may be overly minimized[134]. No other patient characteristics have been consistently associated with receipt of re-excision surgery, although white, non-Hispanic ethnicity was reported to be associated with less re-excision in one study[135].

1.4.4 Provider Characteristics

Significant variation in re-excision rates is associated with the lack of consensus on the margins that require re-excision[136]. A survey of Canadian surgeons found substantial variation in the definition of close and negative margins between surgeons and in the threshold for recommending re-excision[137]. Similar results have been reported from surveys in Europe and the United States[138, 139]. Publication of the 2014 breast conserving surgery margin consensus guideline[122] will hopefully decrease re-excision rates.

Hospital and surgeon caseload are also associated with receipt of re-excision[19, 135, 140]. de Camargo Cancela *et al*[19] found that patients who received surgery in low volume hospitals from low volume surgeons were 56% more likely to require re-excision compared to patients who received surgery in high volume hospitals from high volume surgeons. Patients treated in academic centers are more likely to receive re-excision surgery[128]. Receipt of re-excision is lower when physicians are in solo practice[135].

1.4.5 Geographic Variation

Significant geographic variation in re-excision rates has been reported in England, the Netherlands and in the United States[123, 128, 129, 133]. Jeevan *et al.*[123] report that unadjusted re-excision rates across hospital groups in the Netherlands range from less than 10% to more than 30%; substantial variation in these rates remained after case-mix adjustment. Within Canada, re-excision rates range from 17% of patients in Quebec to 56% in Newfoundland[70, 125]. This variation may be explained in part by the geographic variation in mastectomy rates mentioned previously[70] and due to the absence of consensus on margin status.

1.5 SUMMARY AND MOTIVATION

Investigation and identification of unwarranted variation in cancer services is crucial as it has the potential to inform interventions aimed at improving equitable access to quality services for cancer patients and improve their overall health and quality of life. Clinical, patient, provider and geographic factors have all been significantly associated with variation in the surgical treatment received by breast cancer patients, including initial surgical procedure type and the receipt of re-excision, however there has been very little research in to whether such variation exists in Alberta and Canada.

Beyond the lack of research, there are several other motivating factors for this work. Firstly, the rate of mastectomy for non-metastatic breast cancer in Alberta is very high (56% compared to BC 46%, ON 37%, QC 26%)[70], and we have previously reported significant geographic variation in BCS receipt within the province[84]. We have hypothesized that these results may be associated with characteristics of the operating surgeon, a potentially modifiable source of unwarranted variation. Here we investigate this hypothesis; specifically the association between surgeon volume and surgery type, as well as quantify the residual variation associated with both surgeons and hospitals.

Also, growing population-based evidence, including one study on which I am the first author[141], has begun to suggest that patients who receive BCS and radiotherapy may have better survival compared to those who receive mastectomy[141-144], despite well-established equivalence demonstrated in clinical trials. Results from clinical trials do not always translate to the population, however, as patients involved in trials tend to be younger, healthier and less racially and ethnically diverse than the typical patient population[145]. Also, improvements to surgical and systemic therapies since these trials were conducted may have an influence on relative survival. Therefore, it is possible that at this time treatment with BCS followed by radiotherapy results in better survival than mastectomy. If this is the case, variation associated with surgery type may influence not only patient quality of life, but also patient survival.

In Alberta, a large proportion of patients who receive BCS later receive re-excision surgery[70]. Despite this, however, factors associated with receipt of re-excision surgery are understudied. If the use of BCS increases, perhaps due to new evidence suggesting better survival outcomes, more women may also receive re-excision surgery and be subject to the associated undesirable sequelae. As many factors associated with risk of re-excision are not modifiable, potentially modifiable factors such as those associated with the surgeon and geography, should be investigated to provide insight into ways to reduce the high re-excision rate. We therefore will investigate the association of clinical, provider and geographical factors and receipt of re-excision. This population-based investigation of re-excision receipt in Alberta will also provide strong baseline information for future evaluation of the impact of the new consensus guideline regarding BCS margins released in 2014[122]. A tangential investigation of the association of re-excision with mortality will also be performed, as no quality research has been performed on this relationship[124, 147].

1.6 RESEARCH OBJECTIVES

The primary objectives of this thesis research are to:

1. Describe the type of surgery (breast conserving surgery or mastectomy) received by early stage breast cancer patients in Alberta
    a. Investigate the relationships between clinical, patient, provider (specifically, surgeon volume) and geographical factors and surgery type received
    b. Quantify residual surgeon and hospital-specific residual variation
2. Describe the receipt of re-excision by patients who receive initial breast conserving surgery in Alberta
    a. Investigate the relationships between clinical, patient, provider and geographical factors and receipt of re-excision
    b. Quantify residual surgeon and hospital-specific residual variation
3. Determine whether surgery pattern is associated with all-cause and breast cancer-specific mortality

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CHAPTER 2: USING MULTI-LEVEL MODELS TO EXPLAIN VARIATION IN CLINICAL PRACTICE: SURGEON VOLUME AND THE SURGICAL TREATMENT OF BREAST CANCER

2.1 INTRODUCTION

Most women diagnosed with early stage breast cancer have the option of receiving either breast conserving surgery (BCS) with adjuvant radiotherapy or mastectomy[1-3]. BCS is generally the preferred surgical option because it is less invasive than mastectomy, provides a better cosmetic outcome and a superior quality of life[4-6]. Despite this, the rate of mastectomy is very high in Alberta (56% compared to BC 46%, ON 37%, QC 26%)[7] and we have previously reported significant geographic variation in BCS receipt within the province[8]. We hypothesize that this is due in part to characteristics of the operating surgeon, such as surgeon experience. High surgical provider caseload volumes have been repeatedly associated with improved outcomes, including reduced surgical complications, shorter durations of hospital stay and reduced mortality among patients with various cancer types, including cervical, colorectal, thyroid and breast cancers[9-13]. The purpose of this study was to investigate the relationship between surgeon caseload and surgery type, and variation in the surgical treatment received by early stage breast cancer patients in Alberta, Canada.

2.2 METHODS

2.2.1 Study Population

The Alberta Cancer Registry was used to identify women diagnosed with stage I, II or III breast cancer (International Classification of Diseases for Oncology [ICD-O-3] code c50[14]) from 2002 to 2010 in Alberta, Canada, who received breast cancer surgery. Patients were excluded if: 1) histology was not consistent with a solid breast tumor, including sarcoma, lymphoma, and hematopoietic tumors; 2) the patient had a second primary breast cancer diagnosis prior to surgery; and 3) the patient had another cancer diagnosis within 6 months prior to the breast cancer diagnosis, as this may influence treatment decisions.

2.2.2 Data Sources and Variables

Demographic, clinical and treatment information were obtained from the Alberta Cancer Registry including: date of diagnosis; age at diagnosis; geographic region at diagnosis; cancer stage; estrogen and progesterone receptor (ER/PR) status; tumor size; and nodal status. Cancer stage was determined using the American Joint Committee on Cancer (AJCC) staging rules active in the year the cancer was diagnosed; the 5th edition[15] was used for 2002 and 2003, while the 6th edition[16] was used for years 2004 to 2010. ER/PR status was not collected in years 2002 and 2003, therefore patients diagnosed in those years who received hormone therapy were classified as ER/PR positive, while those who did not receive hormone therapy were classified as ER/PR negative. If ER/PR status was missing in patients diagnosed from 2004 to 2010 (N= 77), the cancer was assumed to be ER/PR positive, since roughly 75% of breast cancers in North America are ER/PR positive[17]. Patients with missing tumor size (N=450) or nodal status (N=175) were randomly assigned a value proportionally based on the non-missing information. The following sensitivity analyses were run to test the assumptions: 1) 25% of patients diagnosed 2004 to 2009 with missing ER/PR status were randomly assigned to be ER/PR negative, 2) patients with missing tumor size were randomly assigned to be T4 and, 3) patients with missing nodal status were assigned to be N3; results of the sensitivity analyses did not differ from the primary analyses. The North American Association of Central Cancer Registries has awarded the Alberta Cancer Registry the highest level of certification in all years of the study for its high level of completeness and for the timeliness of data collection and reporting.

Alberta Health Physician Claims data were used to identify the first breast cancer surgery after diagnosis. Date and type of surgery, surgical hospital and anonymized physician identifier were obtained from this data source.

Surgeon volume was calculated from the number of first breast surgeries performed on patients in the study cohort in each surgeon's highest volume year during the study period. If multiple physician claims existed for the same surgery date for a particular patient, the surgery was counted toward the surgeon who received the most compensation for the procedure. Very high, high, medium, low and very low volume surgeons were defined as those who performed 60 or more, 20-59, 13-19, 5-12 and 1-4 surgeries in their highest volume year, respectively. Categories were defined through exploratory analysis, with the aim to group surgeons with the most similar rates of mastectomy.

2.2.3 Statistical Analysis

Descriptive statistics were calculated for the demographic and clinical characteristics of the study patients by surgeon volume category. Multi-level logistic regression with surgeons and hospitals as crossed random effects was used to estimate odds ratios of receiving mastectomy by surgeon volume, adjusting for year of diagnosis, age at diagnosis, geographic region, ER/PR status, tumor size and nodal status and for interaction of all variables with stage. Post-estimation lincom commands were used to calculate the odds ratios for the variables of interest, by stage. Crossed random effects were necessary as some surgeons operated out of multiple hospitals. Empirical Bayes estimation was used to estimate adjusted odds ratios for individual surgeons and hospitals. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Cary, NC, USA) and Stata 12.1 (Stata Corp LP, TX, USA).

2.3 RESULTS

There were 14,933 patients with stage I, II and III breast cancer diagnosed in Alberta from 2002 to 2010, excluding cases with non-solid tumor morphology and patients who had another cancer diagnosis within 6 months prior to breast cancer diagnosis. Additional patients were excluded for the following reasons: 282 did not receive surgery; 145 were diagnosed with a second primary breast cancer after diagnosis but prior to surgery; and 918 had missing or incomplete billing data. The final cohort consisted of 13,588 breast cancer patients who were treated by 133 surgeons.

Table 2-1 shows the distribution of demographic and clinical characteristics by surgeon volume. Almost half (47%) of all patients received surgery from ten very high volume surgeons. Very high volume surgeons treated a higher percentage of the youngest patient group (50%) compared to the oldest patients (40%). The distribution of stage was similar across surgeons of all volumes. Patients diagnosed in the metropolitan area of Calgary were the most likely to receive surgery from a high or very high volume surgeon (95%), while patients from Edmonton (another metropolitan area), Central, Northern and Southern Alberta were less likely (86%, 71%, 70% and 66%, respectively).

Overall, 51% of patients received mastectomy. The crude rates of mastectomy for patients who received surgery from very high, high, medium, low and very low volume surgeon was 47%, 53%, 58%, 69% and 49%, respectively. Table 1-2 displays the stage-specific adjusted odds ratio estimates of receiving mastectomy. Patients with stage I and stage II breast cancers whose surgery was conducted by a low volume surgeon had about twice the odds of receiving mastectomy as those that had surgery performed by a very high volume surgeon (Stage I OR= 2.36, 95% CI: 1.40, 3.97; Stage II OR= 1.96, 95% CI: 1.13, 3.42); however, the adjusted odds of mastectomy for patients of very low volume surgeons did not differ statistically from that of patients of very high volume surgeons. After adjustment for demographic/clinical characteristics, surgeon volume and interaction with stage, significant variation of the odds of mastectomy for patients of all stages remained between surgeons (OR standard deviation [SD]: 0.56, 95% CI: 0.46, 0.69) and between hospitals (OR SD= 0.19, 95% CI: 0.08, 0.49).

Empirical Bayes odds ratio estimates of the adjusted surgeon and hospital-specific variation are displayed in Figures 2-1A and 2-1B, respectively. Thirteen surgeons had significantly above-average adjusted odd ratios of mastectomy; the three highest odds ratios were 2.70 (95% CI: 2.13, 3.42), 2.50 (95% CI: 1.61, 3.88) and 2.19 (95% CI: 1.35, 3.54). Seventeen surgeons had adjusted odds ratios which were significantly below average. None of the hospitals had significantly above or below average adjusted odds ratios of mastectomy.

2.4 DISCUSSION

In this study, the factors most appropriately associated with surgery type decisions, tumor size, nodal status and age at diagnosis, were the most strongly associated with surgery type received. The effect of non-appropriate factors, patient geography, surgeon volume, and other surgeon-specific factors, was less, but significant. The association with hospital was minimal.

The proportion of patients diagnosed with stage I and II breast cancers in Alberta who received mastectomy was the greatest among those who received treatment from low volume surgeons. This relationship was maintained after adjusting for demographic and clinical characteristics and accounting for variation among surgeons and hospitals. In contrast, the proportion of patients who received treatment from very low volume surgeons was similar to that of very high volume surgeons. We hypothesize that surgeons with very little experience may consult higher volume surgeons about the best surgical care for their patients. Others have speculated that surgeons who perform less than 5 surgeries a year are trainees or visiting physicians[18]. We also hypothesize that surgeon volume was not associated with increased mastectomy receipt among stage III patients because surgical decision-making is simpler among patients with more advanced disease.

Association between low breast surgeon volume and mastectomy has been reported in several geographic contexts including in the US, England and Australia[18-21]. We hypothesize that differing provider beliefs and attitudes about surgical options among surgeons of varying experience is likely responsible for the observed relationship, as patient decisions are strongly influenced by what they perceive their surgeon thinks is best[22]. A US survey performed by Katz *et al.*[23] reported caseload volume to be strongly associated with surgeon opinions about treatment options, with high volume surgeons being more likely to favor BCS plus radiotherapy than low volume surgeons for treatment of invasive breast cancer. Surgical preference was not associated with surgeon perceptions about disease recurrence, but was strongly associated with perceptions about quality of life, with surgeons who favored BCS much more likely to perceive greater quality of life benefits for BCS versus mastectomy compared to surgeons who favored mastectomy. Systematic variation in the care provided to early stage breast cancer patients by volume of the surgeon suggests a lack of consensus on standard practice, despite evidence of better quality of life with BCS plus radiotherapy. It is also possible that the observed relationship between low surgeon caseload and mastectomy is a reflection of the preferences of patients who receive treatment from low volume surgeons.

Surgical care for breast cancer patients provided by individual surgeons was found to vary significantly beyond the variation explained by patient case mix and surgeon volume. Thirteen surgeons were found to perform mastectomy significantly more often than the average surgeon. This residual variation may be attributed to surgeon characteristics and preferences beyond that explained by surgeon volume such as years since graduation, foreign training, specialization and gender, and may also be attributed in part to residual confounding by unmeasured patient case mix variables such as patient socioeconomic status and distance to radiotherapy[19, 21, 24].

Between-surgeon variation in receipt of mastectomy versus BCS was quantified by Hawley *et al.*[25] who surveyed a sample of ductal carcinoma in situ (DCIS) and stage I-III invasive breast cancer patients and their surgeons in the USA from 2001 to 2003. They reported that 10% of variation in surgical treatment is attributable to the surgeon, a large proportion of which is explained by provider factors including surgeon volume, years in practice and practice setting. These factors are not relevant for clinical decision-making and reflect potential sources of the care variation described. This explanation is consistent with empirical observation of breast cancer surgeons who are active in improving the quality of surgical care in Alberta.

This population-based investigation of early stage breast cancer patients in the publicly-funded health care system present in Alberta, Canada provides uniquely valuable information about surgical treatments received within a non-selected patient population with minimal bias caused by variation in access to care often present in alternately-funded health systems. Multi-level modeling was used to account for the hierarchical data structure and empirical Bayes estimation was used to provide more reliable individual surgeon and hospital estimates, which increases the credibility of our results. A limitation of this study was our inability to assess contraindications for breast conserving surgery and the lack of information about patient-level factors, such as socioeconomic status, and surgeon-level factors, due to the nature of the data sources.

Significant variation in the likelihood of BCS by surgeon is concerning given the potential benefits of BCS for those who are eligible. Efforts toward provider behavioral change would likely decrease this variation which may be accomplished through greater emphasis of BCS benefits in continuing surgeon education, reporting of peer practices, and discouraging low volume surgeons from performing breast surgeries. Implementation of appropriate interventions to combat this care variation in Alberta is necessary.

Table 2-1. Characteristics of breast cancer patients diagnosed in Alberta from 2002 to 2010 by surgeon volume

	Surgeon Volume				
	Very High N (%)[1]	**High N (%)[1]**	**Medium N (%)[1]**	**Low N (%)[1]**	**Very Low N (%)[1]**
Total Number of Patients	6324 (47)	5152 (38)	1244 (9)	718 (5)	150 (1)
Total Number of Surgeons	10 (8)	30 (23)	22 (17)	28 (21)	42 (32)
Age at Diagnosis					
<50	1782 (50)	1331 (37)	256 (7)	179 (5)	35 (1)
50-59	1694 (48)	1300 (37)	323 (9)	191 (5)	34 (1)
60-69	1427 (46)	1191 (38)	291 (9)	156 (5)	31 (1)
70-79	993 (43)	892 (39)	247 (11)	132 (6)	35 (2)
80+	428 (40)	438 (41)	127 (12)	60 (6)	15 (1)
Geography at Diagnosis					
Calgary	2161 (43)	2619 (52)	153 (3)	72 (1)	32 (1)
Edmonton	3084 (68)	832 (18)	474 (10)	113 (2)	32 (1)
South	21 (2)	709 (64)	225 (20)	138 (13)	11 (1)
North	540 (44)	320 (26)	114 (9)	197 (16)	44 (4)
Central	518 (31)	672 (40)	278 (16)	198 (12)	31 (2)
Year of Diagnosis					
2002-2004	1538 (38)	1671 (42)	481 (12)	258 (6)	75 (2)
2005-2007	2164 (47)	1730 (38)	445 (10)	236 (5)	35 (1)
2008-2010	2622 (53)	1751 (35)	318 (6)	224 (5)	40 (1)
ER/PR Status					
Positive	5238 (47)	4203 (38)	993 (9)	564 (5)	121 (1)
Negative	1086 (44)	949 (38)	251 (10)	154 (6)	29 (1)
Stage					
Stage I	3154 (48)	2472 (37)	620 (9)	318 (5)	74 (1)
Stage II	2325 (45)	2019 (39)	458 (9)	288 (6)	59 (1)
Stage III	845 (47)	661 (37)	166 (9)	112 (6)	17 (1)
Tumor Size					
T0	9 (56)	5 (31)	0 (0)	2 (13)	0 (0)
T1	3977 (47)	3179 (38)	775 (9)	422 (5)	96 (1)
T2	1897 (45)	1605 (38)	389 (9)	243 (6)	46 (1)
T3	278 (46)	231 (38)	52 (9)	36 (6)	5 (1)
T4	163 (48)	132 (39)	26 (8)	15 (4)	3 (1)
Nodal Status					
N0	4167 (47)	3322 (38)	828 (9)	442 (5)	98 (1)
N1	1512 (45)	1327 (40)	285 (9)	184 (6)	38 (1)
N2	402 (45)	326 (36)	93 (10)	65 (7)	9 (1)
N3	243 (50)	177 (36)	38 (8)	27 (6)	5 (1)
Surgery Type[2]					
Mastectomy	2982 (47)	2711 (53)	720 (58)	493 (69)	74 (49)
BCS	3342 (53)	2441 (47)	524 (42)	225 (31)	76 (51)

[1]Percentages are row percentages, where the denominator is the total number of patients
[2]Surgery type percentages are column percentages, where the denominator is the total number of patients

Table 2-2. Adjusted[1] odds ratio of mastectomy estimates[2] for stage I-III breast cancer patients diagnosed in Alberta from 2002 to 2010

	Adjusted[1] Odds of Mastectomy Estimates[2] (95% CI)		
	Stage I	**Stage II**	**Stage III**
Surgeon Volume	**P= 0.004**	**P= 0.014**	**P= 0.42**
Very High	1.00	1.00	1.00
High	1.14 (0.72, 1.80)	0.92 (0.58, 1.47)	0.91 (0.53, 1.53)
Medium	1.27 (0.77, 2.10)	1.05 (0.63, 1.77)	0.60 (0.32, 1.14)
Low	2.36 (1.40, 3.97)	1.96 (1.13, 3.42)	1.16 (0.56, 2.42)
Very Low	0.94 (0.48, 1.82)	0.77 (0.37, 1.59)	0.91 (0.24, 3.40)
Geography	**P= 0.003**	**P= 0.005**	**P= 0.32**
Calgary	1.00	1.00	1.00
Edmonton	1.24 (0.94, 1.63)	1.05 (0.78, 1.41)	1.18 (0.80, 1.75)
South	1.33 (0.93, 1.89)	1.38 (0.95, 2.01)	1.30 (0.73, 2.32)
North	1.55 (1.13, 2.12)	1.43 (1.02, 2.00)	1.44 (0.85, 2.44)
Central	1.59 (1.21, 2.09)	1.43 (1.06, 1.94)	1.64 (1.00, 2.67)
Age at Diagnosis	**P< 0.001**	**P< 0.001**	**P= 0.008**
<50	1.17 (1.00, 1.37)	1.07 (0.92, 1.25)	1.11 (0.81, 1.50)
50-59	1.00	1.00	1.00
60-69	1.37 (1.19, 1.59)	1.18 (0.99, 1.40)	1.43 (1.00, 2.05)
70-79	1.96 (1.68, 2.29)	2.12 (1.74, 2.58)	2.03 (1.29, 3.19)
80+	2.27 (1.82, 2.83)	2.75 (2.15, 3.52)	1.68 (1.01, 2.78)
ER/PR Status	**P= 0.059**	**P=0.041**	**P= 0.39**
Positive	1.00	1.00	1.00
Negative	1.15 (0.99, 1.32)	1.18 (1.01, 1.37)	1.14 (0.84, 1.55)
Year of Diagnosis	**P= 0.96**	**P= 0.44**	**P= 0.31**
2002-2004	1.00	1.00	1.00
2005-2007	0.98 (0.86, 1.13)	0.93 (0.80, 1.09)	0.82 (0.60, 1.12)
2008-2010	0.98 (0.86, 1.13)	0.91 (0.78, 1.06)	1.00 (0.72, 1.37)
Tumor Size		**P< 0.001**	**P< 0.001**
T0/1	1.00	1.00	1.00
T2	-	2.27 (1.94, 2.65)	2.07 (1.54, 2.79)
T3	-	4.90 (3.24, 7.41)	5.07 (3.29, 7.81)
T4	-	-	14.5 (7.43, 28.2)
Nodal Status		**P< 0.001**	**P< 0.001**
N0	1.00	1.00	1.00
N1	-	1.87 (1.61, 2.16)	8.07 (3.25, 20.0)
N2	-	-	6.29 (2.49, 15.9)
N3	-	-	8.56 (3.35, 21.9)
RE Parameter Estimate (SD)			
Hospital	0.19 (0.08, 0.49)		
Surgeon	0.56 (0.46, 0.69)		

[1]Adjusted for all variables in the table in addition to interaction of all variables with stage
[2]Multi-level logistic regression with hospitals and surgeons as crossed random effects

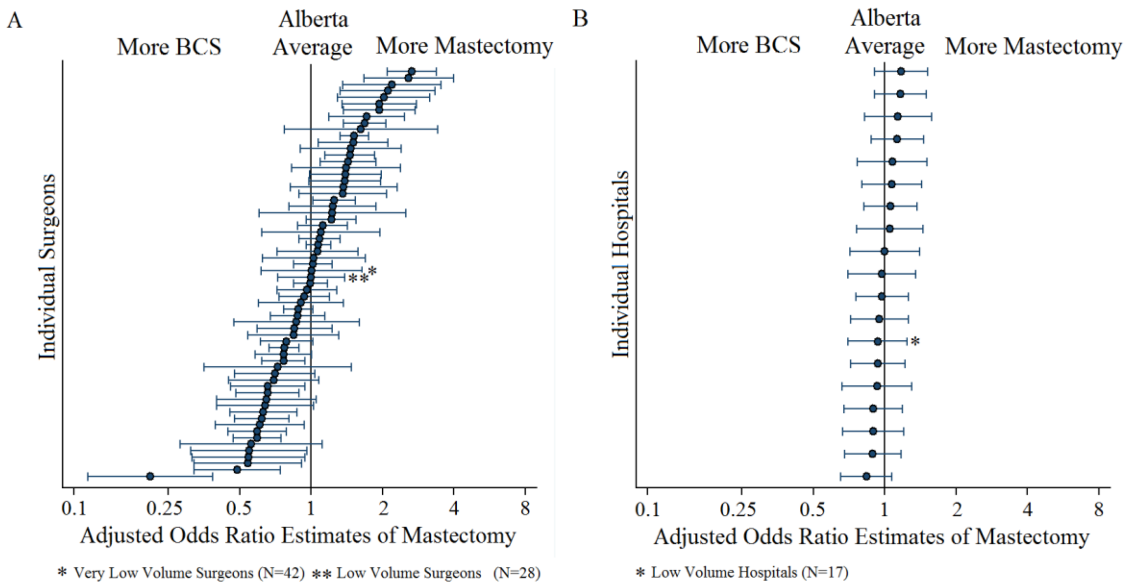

Figure 2-1. Empirical Bayes estimates of adjusted odds ratios of mastectomy for breast cancer patients by (A) individual surgeon, and (B) individual hospital, adjusting for patient characteristics and accounting for variation by surgeon volume

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CHAPTER 3: RE-EXCISION FOLLOWING BREAST CONSERVING SURGERY AND SURVIVAL IN EARLY STAGE BREAST CANCER PATIENTS: A POPULATION-BASED STUDY

3.1 INTRODUCTION

Clinical trials have demonstrated equivalent survival for patients who receive breast conserving surgery (BCS) followed by radiotherapy and mastectomy for the treatment of early stage breast cancer[1, 2]. Since BCS is less invasive, associated with less morbidity and a better cosmetic outcome than mastectomy, BCS with radiotherapy is generally the preferred treatment option[3]. One disadvantage of this treatment over mastectomy, however, is the risk of re-excision, which may be performed if non-negative resection margins remain after the initial surgery. Re-excision is associated with greater morbidity, patient anxiety, poorer cosmetic outcome, delayed initiation of adjuvant therapies, and increased medical cost[4, 5].

Re-excision has not been associated with mortality, although present evidence is lacking and poor in quality[6, 7]. For example, the single population-based study to investigate survival after re-excision did not include an examination of breast cancer-specific mortality and used a flawed definition of survival time that introduced immortal time bias[6]. Further population-based investigation of both all-cause and breast cancer-specific mortality is therefore of interest.

The purpose of this study was to investigate the relationship between re-excision and: 1) clinical, patient, provider and geographical factors and, 2) all cause and breast cancer-specific mortality compared to those who receive BCS without re-excision and those who receive an initial mastectomy, in early stage breast cancer patients diagnosed in Alberta 2002 to 2009.

3.2 METHODS

3.2.1 Study Population

The Alberta Cancer Registry was used to identify women diagnosed with stage I, II or III breast cancer (International Classification of Diseases for Oncology [ICD-O-3] code c50[8]) from 2002 to 2009 in Alberta, Canada. Patients were excluded if: 1) histology indicated the cancer was a sarcoma, lymphoma, or a hematopoietic tumor, 2) the patient did not receive breast cancer surgery, 3) the patient had a second primary breast cancer diagnosis prior to surgery, 4) the patient had another cancer diagnosis within 6 months prior to the breast cancer diagnosis as this may influence treatment decisions, and 5) the patient did not have at least one year of follow-up following initial surgery, which was necessary to ensure complete re-excision exposure ascertainment.

3.2.2 Data Sources and Variables

Demographic, clinical and treatment information were obtained from the Alberta Cancer Registry including: date of diagnosis; age at diagnosis; geographic region at diagnosis; cancer stage; tumor size; nodal status; estrogen and progesterone receptor (ER/PR) status; receipt of neo-adjuvant and adjuvant chemotherapy; receipt of hormone therapy; receipt of post-operative radiotherapy; date of death; and cause of death. Cancer stage was determined using the American Joint Committee on Cancer (AJCC) staging rules active in the year the cancer was diagnosed; the 5th edition[9] was used for 2002 and 2003, while the 6th edition[10] was used for years 2004 to 2009. Patients diagnosed in 2002 and 2003 who received hormone therapy were classified as ER/PR positive, while those who did not receive hormone therapy were classified as ER/PR negative, since ER/PR status was not collected in these years. If ER/PR status was missing in patients diagnosed from 2004 to 2009 (N= 66), the cancer was assumed to be ER/PR positive, since roughly 75% of breast cancers in North America are ER/PR positive[11]. Patients with missing tumor size (N= 194) or nodal status (N= 161) were randomly assigned a value proportionally based on the non-missing information. The following sensitivity analyses were run to test the assumptions: 1) 25% of patients diagnosed 2004 to 2009 with missing ER/PR status were randomly assigned to be ER/PR negative, 2) patients with missing tumor size were randomly assigned to be T4 and, 3) patients with missing nodal status were assigned to be N3; results from the sensitivity analyses did not differ from those of the primary analyses. The North American Association of Central Cancer Registries has awarded the Alberta Cancer Registry the highest level of certification in all years of the study for its high level of completeness and for the timeliness of data collection and reporting.

Alberta Health Physician Claims data were used to identify the first breast cancer surgery after diagnosis and subsequent re-excision procedures up to 1 year after initial surgery. Surgery date, type of surgery, surgical hospital and anonymized physician identifier were obtained from this source. Surgery pattern was classified as BCS without re-excision, BCS followed by re-excision with BCS, BCS followed by re-excision with mastectomy, and initial mastectomy. Type of re-excision was designated as the most final surgery type received. Very high, high, medium, low and very low volume surgeons were defined as those who performed 60 or more, 20-59, 13-19, 5-12 and 1-4 surgeries in their highest volume year, respectively, and was described further in Chapter 2.

3.2.3 Statistical Analyses: Re-excision Receipt

To investigate factors associated with receipt of re-excision, analyses were restricted to patients whose initial surgery was BCS. Descriptive statistics were calculated for the demographic and clinical characteristics of patients by cancer stage. Multi-level logistic regression with surgeons and hospitals as crossed random effects were used to estimate odds ratios of re-excision, stratified by stage, and adjusting for age at diagnosis, geography at diagnosis, surgeon volume, year of diagnosis, tumor size and nodal status. Crossed random effects were necessary as some surgeons operated out of multiple hospitals.

3.2.4 Statistical Analyses: Overall Survival and Breast Cancer-Specific Mortality

Two additional exclusions were made for the investigation of surgery pattern on overall survival and breast cancer-specific mortality: 1) patients who did not receive radiotherapy following BCS and 2) patients who received radiotherapy following mastectomy. These exclusions were made to facilitate comparison of patients who receive standard treatments and because these groups of patients were found to have worse mortality outcomes. Start time was one year following initial surgery, as ascertainment of re-excision surgeries ended at this time. Patients were followed until the earliest of date of death or September 30, 2011.

Descriptive statistics were calculated for the demographic and clinical characteristics of the study patients by surgery pattern. Overall survival and breast cancer-specific mortality of patients by surgical pattern was compared by Kaplan-Meier and cumulative incidence curves, respectively, with deaths from other causes being treated as competing risks in the cumulative incidence analysis. Log-rank and Gray's test statistics were used to assess differences in overall survival and breast cancer-specific mortality, respectively. Poisson regression models were fitted to compare overall survival and breast cancer-specific mortality by surgery pattern, adjusting for geography at diagnosis, year of diagnosis, ER/PR status and hormone therapy, neo-adjuvant and adjuvant chemotherapy, tumor size, nodal status, age during follow-up and time since study start. Multi-level models with surgeons and hospitals as crossed random effects were fit; no residual variation by surgeon or hospital was found, therefore, the most parsimonious model is presented. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Cary, NC, USA) and Stata 12.1 (Stata Corp LP, TX, USA).

3.3 RESULTS

There were 13 032 patients diagnosed with early stage breast cancer from 2002 to 2009 in Alberta, excluding non-solid tumors and patients who had another cancer diagnosis within 6 months prior to their breast cancer diagnosis. Additional patients were excluded for the following reasons: 242 patients did not receive surgery; 115 were diagnosed with a second primary breast cancer prior to surgery; 830 had missing or incomplete billing data; and 210 did not have at least one year of follow-up following initial surgery. The eligible cohort consists of 11 635 patients; a flow chart of surgeries received by the eligible cohort is displayed in Figure 3-1. Initial BCS was received by 5 660 patients who make up the first analysis group. The mortality analysis includes 9 032 patients: from the original eligible cohort a further 517 patients who did not receive radiotherapy after BCS and 2 086 patients who received radiotherapy after mastectomy were excluded.

3.3.1 Receipt of Re-excision

Patient demographic and clinical characteristics and their associations with re-excision following initial BCS are shown in Table 3-1. A total of 1 087 patients (19%) received re-excision surgery; 16%, 23% and 30% of stage I, II and III cancers, respectively. Regardless of stage, the proportion of patients who received re-excision was lowest when the patient was 80+ years of age (9%, 16% and 13% for stage I, II and III breast cancers, respectively) and when the patient was diagnosed in Calgary (13%, 19% and 24% for stage I, II and III breast cancers, respectively).

Table 3-2 displays the stage-specific adjusted odds ratios of re-excision. In contrast to the unadjusted analysis, increasing age was associated with re-excision. Patients in Edmonton, Central and Northern Alberta had significantly greater adjusted odds of re-excision than those in Calgary; stage II patients in Northern Alberta had the greatest odds of re-excision (adjusted OR=2.27, 95% CI: 1.38). Re-excision among stage I (OR standard deviation (SD)= 0.44, 95% CI: 0.31, 0.63) and II (OR SD= 0.43, 95% CI: 0.28, 0.65) patients varied significantly by individual surgeon, beyond the variation explained by the factors investigated.

3.3.2 Overall Survival and Breast Cancer-Specific Mortality

The median follow-up time of the 9 032 patients included in the survival/mortality analyses was 4.0 years. A total of 880 (9.7%) patients died during the follow-up period: 406 (4.5%) from breast cancer and 474 (5.2%) from other causes. Demographic, clinical and treatment characteristics by surgery pattern are displayed in Table 3-3. BCS, BCS followed by re-excision with BCS, BCS followed by re-excision with mastectomy, and mastectomy were received by 45%, 5%, 5% and 45% of patients, respectively. Older patients were most likely to receive mastectomy, both initially and as a re-excision following initial BCS. Re-excision with mastectomy was more prevalent than re-excision with BCS in Central and Southern Alberta, while re-excision by BCS was more prevalent among patients residing in the urban regions (Edmonton and Calgary) and Northern Alberta.

Figure 3-2 shows Kaplan-Meier and cumulative incidence curves for overall survival and breast cancer-specific mortality, respectively, by surgery pattern. Patients who received mastectomy had the greatest risk of all-cause and breast cancer-specific mortality. The overall five-year all-cause survival probabilities for patients who received BCS, BCS followed by re-excision with BCS, BCS followed by re-excision with mastectomy, and mastectomy were 92.5% (95% CI: 91.5%, 93.5%), 94.7% (95% CI: 91.5%, 96.8%), 91.2% (95% CI: 87.8%, 94.3%) and 84.4% (95% CI: 83.0%, 85.7%), respectively. The five-year cumulative incidence of breast cancer-specific death were 3.5% (95% CI: 2.9%, 4.2%), 4.7% (95% CI: 2.7%, 7.6%), 5.3% (95%: 3.1%, 11.1%) and 6.8% (95% CI: 5.9%, 7.8%) for patients who received BCS, BCS followed by re-excision with BCS, BCS followed by re-excision with mastectomy, and mastectomy, respectively.

Adjusted all-cause and breast cancer-specific mortality ratios are shown in Table 3-4. Re-excision with BCS and re-excision with mastectomy were both associated with similar all-cause and breast cancer-specific mortality as BCS without re-excision. Patients who received mastectomy had a significantly greater all-cause (HR= 1.36, 95% CI: 1.16, 1.59) and breast cancer-specific (HR= 1.38, 95% CI: 1.10, 1.74) mortality than those who received BCS without re-excision. Edmonton had a significantly larger all-cause mortality rate (HR= 1.21, 95% CI: 1.03, 1.42), and Southern Alberta had a significantly larger breast cancer-specific mortality rate (HR= 1.41, 95% CI: 1.02, 1.97) compared to Calgary. The adjusted all-cause mortality rate decreased from 2002-2005 to 2006-2009 (HR= 0.83, 95% CI: 0.71, 0.97). No residual variation by surgeon or hospital was found.

3.4 DISCUSSION

The main objective of this study was to evaluate the clinical and health system factors associated with re-excision surgery among early stage breast cancer patients diagnosed 2002 to 2009 in Alberta, and to compare the survival of patients who received re-excision with those who received a single surgical procedure. At least one re-excision procedure was received by 19% of patients who initially received BCS. Receipt of re-excision was associated with age at diagnosis, geography at diagnosis, stage and tumor size.

Additionally, substantial residual variation of re-excision by surgeon was found for patients with stage I and II disease. All-cause and breast cancer-specific mortality were not significantly associated with re-excision by further BCS or by mastectomy compared to BCS without re-excision, and no variation in survival variation by surgeon or hospital was found beyond that explained by clinical, treatment and patient factors.

At the time of this study there was no consensus regarding the best definition of negative surgical margins that adequately reduced the risk of locoregional recurrence following breast conserving surgery[12]. A survey of Canadian surgeons in 2012 found that 40% of surgeons considered a margin negative when 'no tumor cells are seen on the inked margin', while 14%, 29% and 18% of surgeons required 1 mm, 2 mm and 5 mm of clear tissue, respectively[13]. The Society of Surgical Oncology and the American Society of Radiation Oncology recently developed a consensus guideline for stage I and II breast cancer patients who receive BCS followed with whole breast irradiation, which concluded margins wider than 'no ink on tumor' do not further reduce recurrence risk[14]. This previous lack of margin guidelines is likely largely responsible for the geographic and surgeon-specific variation in re-excision receipt seen in this study.

Re-excision was received by 19% of patients. This is a similar proportion to that found in other population-based studies in England, Ireland, the Netherlands, and in Canada as a whole[6, 15-17]. However, significant variation has been reported between Canadian provinces, as 17% to 56% of patients receive additional surgery[17], and international institution-level studies have reported re-excision receipt as low as 6%[18] and as high as 49%[4].

Significant variation in re-excision by geography and by surgeon was found among stage I and II patients in the current study, which is likely also largely explained by the previous lack of consensus regarding surgical margins. Patients diagnosed in the urban region of Calgary were consistently the least likely to receive re-excision (and encouragingly, also had the lowest all-cause and breast cancer-specific mortality hazards); empirical evidence suggests this is due to early encouragement to accept ‘no ink on tumor’ margins. Other regions have since begun to embrace this recommendation. Surprisingly, re-excision was not associated with surgeon volume, as other studies have reported this association[16], however other characteristics of the operating surgeon, such as years since graduation, foreign training and specialization, may be responsible for some of the residual variation by surgeon reported. The residual variation may also be attributed in part to residual confounding by unmeasured patient case mix variables.

Receipt of re-excision was also associated with tumor size and, among patients with stage I disease, younger age at diagnosis. BCS performed on a large tumor is a more technically challenging procedure than that performed on a small tumor as it is more difficult to remove while also optimizing cosmetic outcome. Younger women tend to have more dense breasts, limiting the ability of the surgeon to accurately assess tumor extent preoperatively[19]. It has also been suggested that younger patients value a satisfactory cosmetic result more than older patients and, therefore, the initial excision may be overly minimized[20].

Re-excision by further BCS or by mastectomy was not significantly associated with all-cause or breast cancer-specific mortality compared to patients who received BCS without re-excision. Previous investigation of survival after re-excision has found similar results[6, 7]. Mastectomy, however, was associated with increased all-cause and breast cancer-specific mortality compared to BCS (which our group, and others have reported previously[21-24]) and compared to patients who received re-excision. It is encouraging that no residual variation by surgeon or hospital was found for all-cause or breast cancer-specific mortality.

To our knowledge this is the first population-based study to investigate re-excision and breast cancer-specific survival and to compare survival of re-excision patients to those who receive initial mastectomy. Limitations of the current study are largely due to the nature of the administrative datasets; we did not have information about margin status, cosmetic outcome, recurrence or prognostic factors such as comorbidities, lifestyle factors and socioeconomic status. Additionally, longer follow-up may be necessary to detect survival differences between the surgery BCS and re-excision surgery pattern groups.

Although the survival of patients who received re-excision was not significantly different from those who received a single BCS procedure, the significant variation in the likelihood of re-excision by geography and by individual surgeon is concerning. We suggest efforts toward educating surgeons about the recent consensus guideline to help increase the number of surgeons employing ‘no ink on tumor’ margins’ to help prevent unnecessary re-excision and the associated negative impacts on patient quality of life.

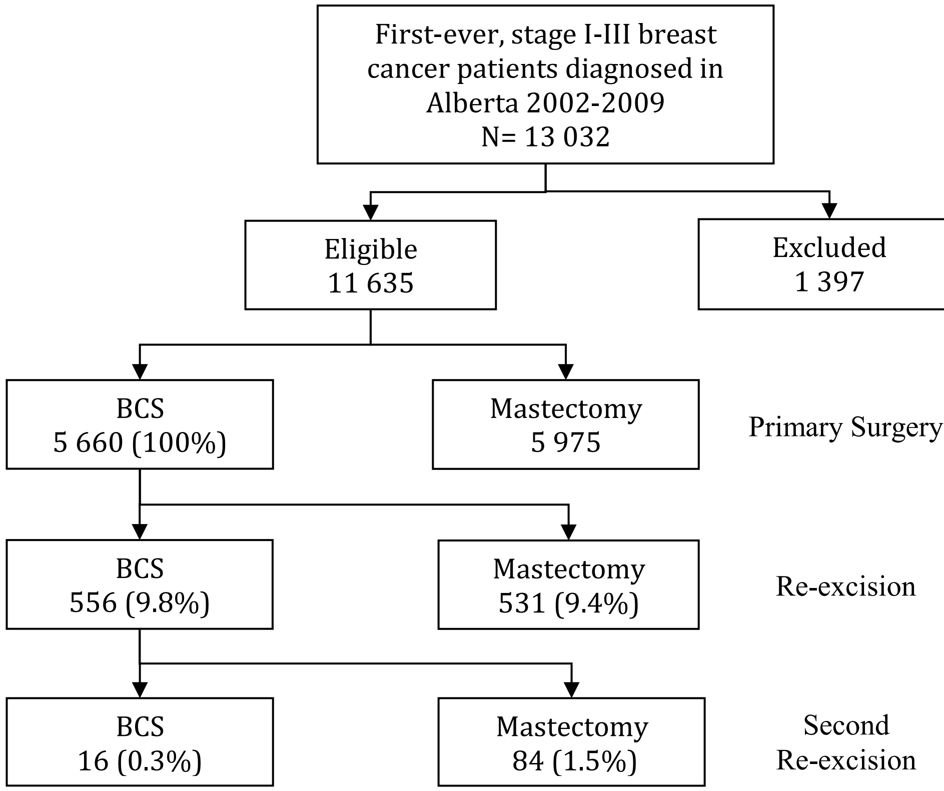

Figure 3-1. Flow chart of breast cancer surgeries received by patients in the eligible cohort

Table 3-1. Characteristics of stage I, II and III breast cancer patients whose initial surgery was BCS by receipt of re-excision

	Stage I		Stage II		Stage III	
	Re-excision Surgery N (%)[1]	Total	Re-excision Surgery N (%)[1]	Total	Re-excision Surgery N (%)[1]	Total
Total Patients	556 (16)	3477	428 (23)	1840	103 (30)	343
Age at Diagnosis						
<50	176 (21)	822	145 (23)	623	42 (34)	125
50-59	166 (16)	1030	133 (25)	535	35 (32)	110
60-69	118 (14)	862	95 (24)	391	16 (25)	64
70-79	79 (14)	581	39 (20)	194	8 (28)	29
80+	17 (9)	182	16 (16)	97	2 (13)	15
Geography at Diagnosis						
Calgary	180 (13)	1373	140 (19)	754	34 (24)	142
Edmonton	223 (17)	1274	157 (26)	610	35 (30)	118
Central	60 (18)	332	39 (21)	185	14 (50)	28
South	46 (19)	238	36 (29)	124	9 (33)	27
North	47 (18)	260	56 (34)	167	11 (39)	28
Surgeon Volume						
Very High (60+)	271 (15)	1760	189 (21)	887	41 (25)	165
High (20-59)	201 (16)	1264	167 (23)	723	39 (33)	119
Medium (13-19)	59 (20)	301	44 (31)	144	19 (49)	39
Low (5-12)	21 (19)	113	21 (33)	63	2 (13)	16
Very Low (<5)	4 (10)	39	7 (30)	23	2 (50)	4
Year of Diagnosis						
2002-2005	253 (15)	1632	202 (25)	802	48 (32)	152
2006-2009	303 (16)	1845	226 (22)	1038	55 (29)	191
Tumor Size						
T0	-	-	0 (0)	1	1 (50)	2
T1	556 (16)	3477	154 (23)	660	21 (18)	118
T2	-	-	258 (22)	1147	49 (31)	157
T3	-	-	16 (50)	32	27 (60)	45
T4	-	-	-	-	5 (24)	21
Nodal Status						
N0	556 (16)	3477	158 (20)	780	2 (18)	11
N1	-	-	270 (25)	1060	14 (48)	29
N2	-	-	-	-	56 (26)	215
N3	-	-	-	-	31 (35)	88

1. The denominator for each percentage is the total number of patients who received initial BCS in the adjacent row for the same stage of disease

Table 3-2. Adjusted[1] odds ratio of re-excision estimates[2] for stage I, II and III breast cancer patients whose primary surgery was BCS

	Adjusted[1] Odds Ratios of Re-excision (95% CI)		
	Stage I	**Stage II**	**Stage III**
Total Patients	3477	1840	343
Age at Diagnosis	**P< 0.001**	**P= 0.44**	**P= 0.34**
<50	1.00	1.00	1.00
50-59	0.68 (0.53, 0.87)	1.06 (0.80, 1.40)	1.04 (0.56, 1.92)
60-69	0.57 (0.44, 0.74)	1.09 (0.80, 1.49)	0.81 (0.37, 1.75)
70-79	0.56 (0.41, 0.75)	0.85 (0.56, 1.29)	0.66 (0.23, 1.84)
80+	0.34 (0.20, 0.58)	0.66 (0.37, 1.20)	0.22 (0.04, 1.25)
Geography at Diagnosis	**P= 0.033**	**P= 0.005**	**P= 0.12**
Calgary	1.00	1.00	1.00
Edmonton	1.76 (1.22, 2.54)	1.96 (1.30, 2.97)	1.87 (0.94, 3.70)
Central	1.62 (1.08, 2.46)	1.22 (0.74, 2.00)	3.68 (1.38, 9.81)
South	1.79 (1.08, 2.96)	1.51 (0.86, 2.66)	1.50 (0.53, 4.21)
North	1.70 (1.07, 2.71)	2.27 (1.38, 3.71)	2.57 (0.91, 7.30)
Surgeon Volume	**P= 0.81**	**P= 0.83**	**P= 0.16**
Very High (60+)	1.00	1.00	1.00
High (20-59)	1.02 (0.68, 1.52)	1.10 (0.72, 1.68)	1.54 (0.78, 3.03)
Medium (13-19)	1.04 (0.64, 1.71)	1.27 (0.74, 2.20)	2.17 (0.85, 5.56)
Low (5-12)	1.05 (0.56, 1.99)	1.41 (0.70, 2.83)	0.32 (0.05, 1.86)
Very Low (<5)	0.54 (0.17, 1.65)	1.45 (0.52, 4.00)	1.94 (0.23, 16.3)
Year of Diagnosis	**P= 0.41**	**P= 0.33**	**P= 0.31**
2002-2005	1.00	1.00	1.00
2006-2009	1.09 (0.89, 1.32)	0.85 (0.67 1.08)	0.76 (0.44, 1.30)
Tumor Size		**P< 0.001**	**P< 0.001**
T0/T1	1.00	1.00	1.00
T2	-	1.40 (1.05, 1.87)	1.90 (1.03, 3.52)
T3	-	6.20 (2.74, 14.0)	8.06 (3.00, 21.7)
T4	-	-	1.70 (0.29, 10.1)
Nodal Status		**P= 0.002**	**P= 0.74**
N0	1.00	1.00	1.00
N1	-	1.76 (1.31, 2.35)	1.29 (0.14, 12.0)
N2	-	-	1.21 (0.11, 13.3)
N3	-	-	1.69 (0.15, 18.7)
RE Parameter Estimates (SDs)			
Hospital	0 (-)	0 (-)	0.17 (0.01, 5.35)
Surgeon	0.44 (0.31, 0.63)	0.43 (0.28, 0.65)	0 (-)

[1]Adjusted for the variables in the table

[2]Multi-level logistic regression with hospitals and surgeons as crossed random effects

Table 3-3. Characteristics of breast cancer patients by surgery pattern

	Surgery Pattern			
	BCS N (%)[1]	**BCS, BCS** N (%)[1]	**BCS, Mastectomy** N (%)[1]	**Mastectomy** N (%)[1]
Total Patients	4090 (45)	438 (5)	426 (5)	4078 (45)
Breast Cancer Deaths	132 (3.2)	17 (3.9)	18 (4.2)	239 (5.9)
All-Cause Deaths	272 (6.7)	19 (4.3)	31 (7.2)	558 (13.7)
Age at Diagnosis				
<50	1138 (50)	129 (6)	152 (7)	861 (38)
50-59	1238 (53)	142 (6)	119 (5)	850 (36)
60-69	996 (47)	108 (5)	82 (4)	924 (43)
70-79	595 (36)	51 (3)	53 (3)	946 (58)
80+	123 (19)	8 (1)	20 (3)	497 (77)
Geography at Diagnosis				
Calgary	1746 (50)	157 (4)	144 (4)	1469 (42)
Edmonton	1424 (49)	163 (6)	155 (5)	1165 (40)
Central	375 (34)	39 (4)	49 (4)	642 (58)
South	239 (32)	35 (5)	42 (6)	436 (58)
North	306 (41)	44 (6)	36 (5)	366 (49)
Year of Diagnosis				
2002-2005	1864 (45)	193 (5)	204 (5)	1905 (46)
2006-2007	2226 (46)	245 (5)	222 (5)	2173 (45)
Stage				
Stage I	2618 (49)	273 (5)	255 (5)	2155 (41)
Stage II	1260 (38)	148 (5)	164 (5)	1715 (52)
Stage III	212 (48)	17 (4)	7 (2)	208 (47)
Tumor Size				
T0	1 (25)	0 (0)	0 (0)	3 (75)
T1	3166 (50)	337 (5)	307 (5)	2550 (40)
T2	887 (36)	95 (4)	115 (5)	1369 (56)
T3	26 (20)	5 (4)	3 (2)	96 (74)
T4	10 (14)	1 (1)	1 (1)	60 (83)
Nodal Status				
N0	3167 (46)	324 (5)	334 (5)	3070 (45)
N1	727 (41)	99 (6)	86 (5)	872 (49)
N2	140 (56)	11 (4)	5 (2)	94 (38)
N3	56 (54)	4 (4)	1 (1)	42 (41)
ER/PR Status and Hormone Therapy				
ER/PR positive & received hormone	2842 (47)	318 (5)	291 (5)	2567 (43)
ER/PR positive & no hormone	542 (39)	45 (3)	64 (5)	727 (53)
ER/PR negative	706 (43)	75 (4)	71 (4)	784 (48)
Neo-adjuvant Chemotherapy				
Not received	4038 (46)	421 (5)	387 (4)	4006 (45)
Received	52 (29)	17 (9)	39 (22)	72 (40)
Adjuvant Chemotherapy				
Not received	2620 (43)	280 (5)	295 (5)	2856 (47)
Received	1470 (49)	158 (5)	131 (4)	1222 (41)

1. Row percentages

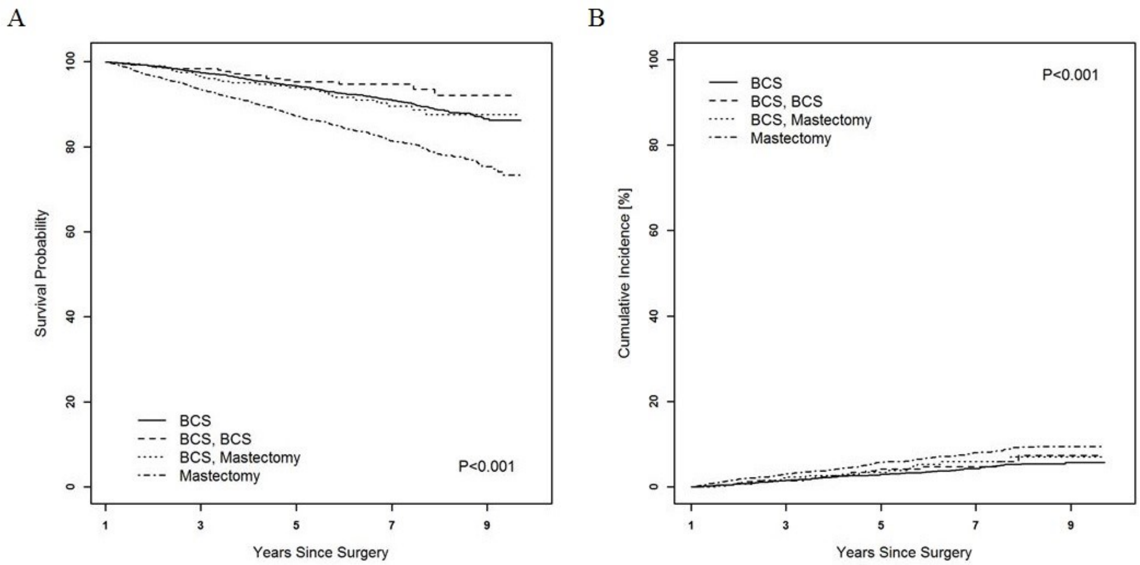

Figure 3-2. Kaplan-Meier survival probabilities (A) and cumulative breast cancer mortality (B) by surgery pattern for stage I-III breast cancer patients

Table 3-4. Adjusted[1] Poisson regression models assessing all-cause and breast cancer-specific mortality by surgery pattern for stage I-III breast cancer patients

	Adjusted[1] Mortality Rate Ratio (95% CI)	
	All-Cause	**Breast Cancer-Specific**
Surgery Pattern	**P< 0.001**	**P= 0.052**
BCS	1.00	1.00
BCS, BCS	0.69 (0.43, 1.19)	1.20 (0.72, 2.00)
BCS, Mastectomy	0.95 (0.65, 1.38)	1.25 (0.76, 2.06)
Mastectomy	1.36 (1.16, 1.59)	1.38 (1.10, 1.74)
Geography at Diagnosis	**P= 0.11**	**P= 0.15**
Calgary	1.00	1.00
Edmonton	1.21 (1.03, 1.42)	1.20 (0.94, 1.53)
Central	1.11 (0.89, 1.37)	1.02 (0.74, 1.41)
South	1.24 (0.98, 1.57)	1.41 (1.02, 1.97)
North	1.27 (0.98, 1.63)	1.36 (0.96, 1.94)
Year of Diagnosis	**P= 0.022**	**P= 0.87**
2002 – 2005	1.00	1.00
2006 – 2009	0.83 (0.71, 0.97)	0.98 (0.77, 1.24)
ER/PR Status & Hormone therapy	**P < 0.001**	**P< 0.001**
ER/PR positive & received hormone	1.00	1.00
ER/PR positive & no hormone	1.52 (1.25, 1.85)	1.26 (0.89, 1.77)
ER/PR negative	1.97 (1.68, 2.30)	2.63 (2.11, 3.26)
Neo-adjuvant Chemotherapy	**P= 0.13**	**P= 0.042**
Not received	1.00	1.00
Received	0.74 (0.51, 1.08)	0.62 (0.40, 0.97)
Adjuvant Chemotherapy	**P= 0.002**	**P= 0.47**
Not received	1.00	1.00
Received	1.38 (1.12, 1.70)	1.11 (0.84, 1.46)
Tumor Size	**P< 0.001**	**P< 0.001**
T0/T1	1.00	1.00
T2	2.13 (1.83, 2.48)	2.37 (1.89, 2.98)
T3/T4	3.02 (2.24, 4.07)	4.40 (3.00, 6.46)
Nodal Status	**P< 0.001**	**P< 0.001**
N0	1.00	1.00
N1	1.81 (1.53, 2.14)	2.38 (1.87, 3.03)
N2/N3	3.02 (2.35, 3.88)	4.57 (3.30, 6.32)

1. Adjusted for all variables shown in the table, in addition to age during follow-up and time since study start

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CHAPTER 4: SUMMARY AND IMPLICATIONS

4.1 OVERALL SUMMARY

Variation in clinical practice is a common and often justified occurrence. However, inappropriate variation associated with a negative impact on care should be identified and eliminated when possible. Our objective was to investigate variation associated with the surgical treatment of breast cancer in Alberta, specifically that is associated with surgical procedure type (Chapter 2) and receipt of re-excision surgery (Chapter 3). The ultimate aim of this of research was to identify sources of variation to help inform policies and interventions aimed at minimizing inappropriate practice variation and improving the quality of services provided to this cancer population.

Clinical, patient, provider and geographic factors were associated with both surgical procedure type and re-excision surgery among breast cancer patients in Alberta and significant surgeon-specific residual variation in these outcomes was observed. Receipt of mastectomy was inversely related to surgeon volume among patients with stage I and II cancer. These results are consistent with previous research investigating variation in the surgical treatment of breast cancer[1-7].

This population-based investigation of type of surgery received by breast cancer patients in the publicly-funded health care system present in Alberta, Canada provides uniquely valuable information about surgical treatments received within a non-selected patient population with minimal bias caused by variation in access to care often present in alternately-funded health systems. The use of multi-level modeling methods to account for the hierarchical data structure and empirical Bayes estimation to provide reliable estimates of surgeon and hospital-specific odds of mastectomy increases the credibility of our results. Limitations of this study are largely due to the nature of the administrative data sources utilized; we were unable to investigate and adjust for relevant clinical factors that may be associated with appropriate variation of the outcomes of interest such as comorbidities and patient-level factors such as socioeconomic status and surgical procedure preference. We were also unable to investigate many potential sources of provider-associated variation, such as that associated with provider training and gender.

4.2 IMPLICATIONS FOR POLICY AND CLINICAL PRACTICE

Within a publicly funded health care system, factors such as surgical provider and region of residence should not be significantly related to patterns of treatment uptake, beyond that explained by patient case-mix and care demand. Surgeon-level variation appears to be caused in part by the influence of the surgeon's previous and current training environments, their clinical experience and knowledge and other contextual factors, many of which are difficult to quantify. Efforts toward provider behavioral change will likely decrease some of the provider-associated variation observed which may be accomplished through continuing surgeon education, the use of performance indicators and decision aids, and policy implemention[8]. For example, efforts have been made to address urban/rural geographic variation in Canada through the attraction and retention of health care providers to rural and remote regions through the Rural and Remote Access Fund[9].

Reduction of the variation associated with receipt of re-excision may be achieved through the implementation of re-excision rate as a performance indicator. This is currently in place in the Netherlands, where 'percentage of patients in whom cancer tissue was left behind after a first breast-conserving operation' is used to evaluate the relative performance of hospitals[7]. The use of re-excision rate as a measure of care quality is controversial, however, as unintended consequences such as the excision of larger volumes of tissue than is necessary leading to worse cosmetic outcomes, or the omission of necessary re-excision resulting in more local recurrences may occur[10-12]. Re-excision variation may also be reduced through local level efforts to increase physician awareness of the new margin consensus guideline[13]. At the Virginia Commonwealth University in the United States an institution-wide policy of 'no tumor on ink' margins for BCS has been in place since 2001, which has resulted in favourable recurrence rates and minimization of re-excision procedures[14].

Since most patients can receive either BCS followed by radiotherapy or mastectomy for the surgical treatment of breast cancer, surgical procedure type is a preference-sensitive treatment. Implementation of decision aids to encourage shared decision making therefore has the potential to reduce the observed variation in surgical procedure type received in Alberta[15, 16]. Although there are no studies that have assessed whether the introduction of decision aids can reduce variation in surgical procedure rates, there is evidence in breast cancer that the use of decision aids increases patient knowledge about their surgical choices, is associated with less decisional conflict and leads to patients being more satisfied with their decisions[15, 17].

4.3 FURTHER RESEARCH

Health service evaluation research such as this plays key roles in extracting evidence from population-based healthcare data and informing health policy makers and other stakeholders in an engaging manner for potential system-wide interventions for improvements. Further research such as this has the potential to improve the care provided by the Canadian health care system. Specifically, further research into patient preferences associated with surgical procedure type is of interest, as well as means to accurately measure this important source of warranted clinical variation. Also of interest is the future evaluation of how the new BCS margin consensus guideline impacts re-excision rates and the variation observed in this study[13].

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