THE INCIDENCE, MANAGEMENT, AND OUTCOME OF INFLAMMATORY BREAST CANCER

by

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Abstract

Background: Inflammatory breast cancer (IBC) is a rare form of breast cancer associated with a poor prognosis. This study describes the incidence, survival, and management of IBC in the province of Ontario.

Methods: We conducted a retrospective, population-based, cohort study using data systems held at the Division of Cancer Care and Epidemiology at Queen's University in Kingston, Ontario. Using the Ontario Cancer Registry (OCR), we identified all primary, pathologically confirmed cases of breast cancer. IBC cases were identified using the unique histology code '85303'. OCR records were linked to Statistics Canada data, Canadian Institutes of Health Information (CIHI) records of surgical procedures, and cancer centre records detailing radiotherapy and chemotherapy administration. We calculated age-adjusted incidence rates of IBC for cases diagnosed between 1984 and 2005. Using the Kaplan Meier product-limit method and log-rank statistics we compared overall survival for IBC and non-IBC, and assessed temporal and regional variations in IBC survival. We described the management of IBC for patients diagnosed between 1984 and 2004, and assessed variations over time and across cancer centres.

Results: Age-adjusted incidence rates of IBC increased from $0.57/10^5$ women-years in 1984-1987 to $1.15/10^5$ women-years in 2003-2005 ($p<0.0001$). 10-year survival was 21.5% for IBC compared to 61.7% for non-IBC ($p<0.0001$). For IBC, 10-year survival increased from 12.0% (95% CI: 8.3–16.3) for those diagnosed between 1984-1994 to 24.0% (95% CI: 20.1–28.2) for those diagnosed between 1995-2005. The utilization of combined mastectomy and postoperative radiotherapy increased from 28.9% in 1984-

1994 to 46.1% in 1995-2004 ($p<0.0001$). We observed no statistically significant difference in the utilization of chemotherapy over time. Differences in the utilization of combined mastectomy and postoperative radiotherapy were observed across cancer centres (29.8% at centre C vs. 54.7% at centre A, $p<0.0001$). We also observed wide variations in the estimates of survival across cancer centres.

Discussion: Rates of IBC have increased over time in Ontario and we observed an improvement in the long-term survival. Management has shifted over time towards increased use of mastectomy and postoperative radiotherapy. Additional prognostic information is needed to determine how variations in practice may be related to variations in outcome.

Co-Authorship

This thesis is an embodiment of the research of John Fralick. The enclosed manuscripts are co-authored with his thesis supervisors, Dr. William J. Mackillop, Dr. Wendy R. Parulekar, and Dr. Patti A. Groome.

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Chapter 1
Introduction

1.1 General Introduction and Rationale

Inflammatory breast cancer (IBC) is a rare form of breast cancer that is associated with poor survival rates[1]. There is limited information at the population level with respect to the incidence, outcome, or management of IBC, largely due to the rarity of this disease.

To date, no study has addressed the incidence, survival, or management of IBC for patients living in Ontario and so there is the opportunity to provide new information for this population. Ontario has the largest population in Canada and accounts for almost 38% of all breast cancers diagnosed in the country[2]. The large number of breast cancer diagnoses in Ontario may allow for a greater opportunity to observe cases of IBC.

There is a lack of randomized-controlled trial (RCT) evidence for IBC management. A lack of RCT data can be indicative of a greater likelihood of practice variations in the management of the disease, especially when more than one treatment option is available[3, 4]. In general, IBC requires a multimodal treatment approach involving chemotherapy, radiotherapy, surgery, and endocrine therapy[5].

1.2 Objectives

The first objective was to describe the incidence and survival of IBC in Ontario for patients diagnosed between 1984 and 2005, and to explore temporal variations in survival. The second objective was to describe the utilization of radiotherapy, surgery, and chemotherapy for the management of IBC. Variations in management were explored

over time and across cancer centres, and we also explored variations in outcome. The final objective of this thesis was to explore aspects of treatment effectiveness based on the variations in management that we observed, using the instrumental variables approach[6].

1.3 Thesis Outline

The second chapter provides a review of the literature related to what is currently known about the incidence, survival, and management of IBC. This thesis includes two manuscripts. The third chapter contains manuscript one, which describes the incidence and survival of IBC for patients residing in Ontario. In addition, temporal variations in survival were explored. This manuscript was prepared based on the submission guidelines for the journal *Cancer*. The fourth chapter contains manuscript two, which describes temporal and regional variations in the utilization of mastectomy, radiotherapy, and chemotherapy, and explores variations in outcome. This manuscript was prepared based on the submission guidelines for the journal *Breast Cancer Research and Treatment*. The fifth chapter provides a discussion of the key findings from the two manuscripts and discusses the strengths, limitations, and implications of this research. The sixth chapter provides an appendix of supplementary results including power and sample size calculations, and an exploration into possible bias related to study exclusion criteria.

1.4 References

1. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: A review. *J Clin Oncol*. 1992;10: 1014-1024.

2. Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2008. 2008.

3. Chassin MR, Brook RH, Park RE et al. Variations in the use of medical and surgical services by the medicare population. *N Engl J Med*. 1986;314: 285-290.

4. Wennberg JE, Gittelsohn A. Variations in medical care among small areas. *Sci Am*. 1982;246: 120-136.

5. Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *Can Med Assoc J*. 2004;170: 983-994.

6. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29: 722-729.

Chapter 2
Literature Review

2.1 Introduction

Breast cancer is a major societal problem. It is the most commonly diagnosed cancer in Canadian women, and in 2008 there were 22 400 new cases[1]. The incidence rate of breast cancer has been fairly stable over the past 20 years and in 2008 the age-adjusted incidence rate was approximately 100 cases per 100 000[1]. In Ontario, breast cancer is a leading cancer cause of premature death in women, ranking second next to lung cancer in years of potential life lost[2].

There are a number of modifiable and non-modifiable factors associated with increased risk of developing breast cancer. Non-modifiable risk factors include reproductive and menstrual history and family history of breast cancer[3]. A number of hormonal factors associated with increased endogenous reproductive hormones are known to increase the risk of developing breast cancer including, early age at menarche, late menopause, and nulliparity[4]. Family history of breast cancer refers to having a first-degree relative (mother, daughter, sister) with breast cancer. Modifiable risk factors include post-menopausal hormone use, weight gain, and physical activity[5]. Analyses by Sprague *et al.* provide summary estimates of the population attributable risk (PAR) for developing breast cancer after menopause. The PAR associated with modifiable risk factors was 40.7% and the summary PAR associated with non-modifiable risk factors was 57.3%[6].

The two most commonly diagnosed types of breast cancer are invasive ductal carcinoma, which accounts for approximately 65 - 80% of cases, and invasive lobular carcinoma, which accounts for approximately 5 - 10% of cases[3]. Inflammatory breast cancer (IBC), which is a rare form of advanced breast cancer, is the subject of this thesis.

All breast cancers can be staged using the TNM staging system[7]. The 'T' category corresponds to the size of the underlying tumour. The 'N' category describes the level of involvement of regional lymph nodes. The 'M' category indicates whether or not the cancer has spread to distant organs. The breast cancer stage is then assigned by combining the tumour size, lymph node status, and metastatic status categories. In general, stage I and II represent early stage breast cancer, and stage III and IV represent advanced stage breast cancer.

2.2 Definition of Inflammatory Breast Cancer

The definition of IBC is somewhat controversial[8]. The signs and symptoms of IBC were first described in 1816 by Sir Charles Bell[9], and IBC was finally defined in 1924 by Lee and Tannenbaum[10]. The component of 'inflammatory' in IBC does not refer to a true state of inflammation but instead it is a reflection of the clinical skin changes that occur in the breast, which resemble an inflammatory process[11].

Clinically, patients with IBC typically present with diffuse erythema and edema of the breast, often without a palpable lump and there is often a sudden onset of increased breast size[7]. It has been recognized that the invasion of the dermal lymphatic vessels of the breast by tumour cells is an important pathological feature of IBC and is thought to

contribute to the clinical skin changes observed[11]. It was Thomas Bryant who, in 1887, first recognized that invasion of the dermal lymphatic vessels produced the clinical signs of inflammation[12, 13].

Currently, the most widely used definition of IBC is that of the American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) which considers IBC to be a clinicopathologic entity[7]. IBC can be classified using the TNM staging system and is assigned the T classification of "T4d"[7], indicating that the clinical features of erythema and edema are present. IBC can also be classified pathologically (based on evidence of dermal lymphatic invasion) using the International Classification of Diseases for Oncology (ICD-O) code M8530/3[14]. Patients with IBC often present with positive regional lymph node disease and IBC patients have been found to be more likely to present with distant metastatic disease compared to non-IBC patients[15]. Under the TNM system, IBC patients who do not show signs of distant metastatic disease would be given a stage grouping of stage IIIB or IIIC, depending on the extent of nodal disease. IBC is typically included under the umbrella term of locally advanced breast cancers.

2.3 Epidemiology

2.3.1 Incidence and Mortality

Population-based studies report that between 1.5% and 2.0% of all breast cancers are IBC[12, 15, 16] when defined clinically. When defined using the conservative pathological definition, population-based studies report that between 0.1% and 1.0% of all breast cancers are IBC[15, 17, 18]. Two studies have looked at the changing incidence rate of IBC

over time using data from the SEER (Surveillance, Epidemiology, and End Results) program. The first study compared the incidence of pathologically confirmed IBC between 1975-1977 and 1990-1992 and found that the overall age-adjusted incidence rate of IBC had doubled from 0.3 cases per 100 000 person-years to 0.7 among white women[17]. Rates increased among African American women from 0.6 to 1.1 cases per 100 000 person-years. The second study, which did not stratify by race, reported a 25% increase in the age-adjusted incidence rate of IBC between the 3-year time intervals 1988-1990 and 1997-1999, from 2.0 to 2.5 cases per 100 000 women-years, respectively[15]. This second study defined IBC based on SEER's 'extent of disease' codes, which provide tumour definitions similar to those of the AJCC/UICC[19].

In other countries, a few single-institutional studies have reported the proportion of breast cancers that are IBC. Higher rates of IBC have been reported in Tunisia, where IBC accounts for approximately 5% to 7% of all breast cancer diagnoses[20]. A retrospective study from Turkey reported that between 1988 and 2000 IBC made up 5% of all breast cancer diagnoses[21]

There are no data available on the mortality associated with IBC.

2.3.2 Etiology

Very little is known about the causes of IBC, and most epidemiological studies report risk factors in which the comparison group is non-IBC. It has consistently been shown that IBC patients are diagnosed at a younger average age than patients with non-IBC[15, 17, 18]. Hance *et al*. reported that the median age at diagnosis was 58 years

(Interquartile range[IQR]= 47 – 70) for IBC and 63 (IQR= 50 – 73) for non-advanced breast cancers[15]. Although women with IBC are typically younger at diagnosis than women with non-IBC the relationship between premenopausal status and IBC has not been consistently linked[12].

A case-control study by Bonnier *et al.* looking into reproductive factors compared pregnancy-associated breast cancer (breast cancer diagnosed during pregnancy or in the first 6 months post-partum) with non-pregnancy-associated breast cancer and found that rates of IBC were significantly higher in the pregnancy-associated group (26% in pregnancy-associated group vs. 9.1% in non-pregnancy-associated group, $p<0.0001$)[22].

It has also been shown that IBC is more common in black women compared to white women[15, 17, 18], and that black women are typically diagnosed with IBC at an earlier age than white women[15, 17]. Although the association between race and risk of IBC has been explored, the relationship between other indicators of socio-economic status (SES) and risk of developing IBC has not been studied. However, a number of studies have observed that lower SES is associated with advanced breast cancer stage at presentation[23-25]. One study, by Merkin *et al.* used an ecological measure of SES based on neighborhood income and education levels and found higher rates of advanced-stage disease in neighborhoods with lower levels of education and income[24].

Chang *et al.*, using a small, single centre case-control study, analyzed different characteristics in women with IBC and compared them to women with non-IBC, and separately to women with non-breast cancer cancers. High BMI (defined as the highest

tertile) was significantly associated with an increased risk of IBC compared to non-IBC and non-breast cancer patients[26]. Women in the highest tertile relative to the lowest had significant increased IBC risk (IBC vs. non-IBC, odds ratio of 2.45 [95% CI: 1.05 – 5.73]. Comparing between IBC and non-breast cancer, they observed an adjusted odds ratio of 4.52 (1.85 – 11.04). They also found that patients with IBC had higher rates of familial breast cancer (13%) compared to those with non-IBC (8%) and non-breast cancers (7%), although this difference was not statistically significant[26]. No significant associations with respect to smoking status and alcohol consumption were observed comparing IBC to non-IBC patients and IBC to non-breast cancer patients.

There is continued exploration into genetic determinants of the IBC phenotype. One gene in particular, RhoC GTPase, which is involved in cytoskeleton restructuring, is thought to contribute to the rapidly progressing features of IBC. Comparisons between IBC tumour specimens and non-IBC tumour specimens found that RhoC GTPase genes were over-expressed in 90% of the IBC specimens compared with 38% in the non-IBC specimens[27].

2.3.3 Prognostic Factors

Positive axillary lymph nodes, metastatic disease at the time of diagnosis, and tumours that are hormone receptor negative are known to be important indicators of a poorer prognosis[7]. Anderson *et al.* showed using SEER data that: 56% of IBC cases had positive lymph nodes at presentation compared with 27.6% of non-IBC cases, 23% of IBC cases had metastatic disease at presentation compared with 4% of non-IBC cases,

and IBC cases had higher rates of tumours with negative hormone receptors compared with non-IBC cases [12]. Being diagnosed with breast cancer at a younger age, a characteristic of IBC, is also associated with a poorer prognosis[28]. As mentioned above, low SES has been shown to be associated with advanced stage disease. Although not specific to IBC, SES has also been shown to be associated with overall and cancer-specific survival in breast cancer, with those breast cancer patients living in communities with the highest income having significant survival advantage compared with those patients living in the poorest income communities[29, 30].

2.4 Treatment Strategies

2.4.1 Surgery

The goal of surgery is to obtain local control and improve survival[31]. Historically, IBC was treated only with mastectomy (the surgical removal of the breast) and had very poor outcomes. The poor outcome following surgery was first recognized in the 1920s[10]. A review of 293 IBC patients managed with mastectomy alone by Kell and Morrow found that the average 5-year overall survival rate was less than 5%[32]. For some women with non-IBC breast-conserving surgery (where only a portion of the breast is removed) is a viable treatment option[33]. However, the use of breast-conserving surgery is not a standard approach for women with IBC due to the non-localized form of disease presentation[34], and a high probability of local recurrence[31].

2.4.2 Radiotherapy

Given the poor results of surgery on its own, radiotherapy with or without surgery was the primary management approach up until the 1970's[32]. The goal of radiotherapy is to decrease the likelihood of recurrence in the breast and regional nodal areas following surgery[35]. Jaiyesimi *et al.* reviewed the results of studies investigating survival in IBC patients treated with radiotherapy alone, and radiotherapy plus surgery. The mean survival for those patients treated with radiotherapy alone ranged from 4 to 33 months and the 5-year overall survival ranged from 0 to 28%[36]. The mean survival for patients treated with both radiotherapy and surgery ranged from less than 12 months to 29 months, with 5-year overall survival ranging from 0 to 20%[36].

2.4.3 Systemic Treatment – Chemotherapy & Endocrine Therapy

Given the poor results observed with radiotherapy and surgery and the systemic nature of the disease, chemotherapy has become an integral part of the modern management of IBC. For locally advanced breast cancer (and IBC), chemotherapy is typically administered in the neoadjuvant (before surgery) and/or adjuvant (after surgery) setting. There are a number of hypothesized benefits to using neoadjuvant chemotherapy in this patient population[37]. By administering neoadjuvant chemotherapy one is able to treat clinically undetectable micrometastatic disease. Additionally, neoadjuvant chemotherapy can help to shrink the primary tumour to improve the likelihood of successful surgical removal. This strategy also provides oncologists with an *in vivo* assessment of the responsiveness of the tumour to systemic treatment agents. The

responsiveness of a tumour to neoadjuvant chemotherapy is another important prognostic factor for long-term disease-free survival[38].

Beginning in the late 1970s retrospective studies were published that incorporated different chemotherapeutic agents into the management of IBC[36]. A number of different chemotherapeutic agents have been studied based on treatment standards for non-IBC. This list includes: cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, epirubicin, and more recently, paclitaxel and, the molecularly targeted therapy, trastuzumab. Combination therapy with chemotherapies involves agents with different mechanisms of action and non-overlapping toxicities as a means of maximizing anti-tumour activity and tolerability. Recommendations concerning the most appropriate chemotherapy regimens for IBC are generally based on evidence from RCTs involving metastatic breast cancer and axillary node-positive breast cancer. Beginning in the late 1980s and 1990s randomized controlled trial (RCT) evidence was published comparing methotrexate-based chemotherapy with anthracycline-based (doxorubicin and epirubicin) chemotherapy in women with non-IBC[39]. In general, anthracycline-based combination chemotherapy has been shown to be superior to methotrexate-based. For example, among women with non-IBC, node-positive breast cancer, one trial showed an improvement in disease free and overall survival associated with the use of epirubicin-based chemotherapy (epirubicin + cyclophosphamide + 5-fluorouracil) versus methotrexate-based (methotrexate + cyclophosphamide + 5-fluorouracil)[40]. In general, single institutional studies on the multimodal management of IBC commonly use anthracycline-based chemotherapy regimens.

For example, a study by Veyret *et al.*[41] reported on the 10-year results of 120 patients with IBC treated with high dose FEC (5-fluorouracil, epirubicin, and cyclophosphamide) in addition to surgery and/or radiotherapy, with some patients receiving additional adjuvant FEC. The 10-year disease free survival was 35.7% and the 10-year overall survival was 41.2%. Another retrospective study at M.D. Anderson used varying doxorubicin-based therapies and found that management with trimodality therapy (that is, a combination of surgery, radiotherapy, and chemotherapy) resulted in 5- and 10-year overall survival rates of 40% and 33%, respectively[42].

Cristofanilli *et al.* examined the use of a newer agent, paclitaxel, in the multimodality treatment for IBC[43]. Patients were also treated with four cycles of neoadjuvant FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) in combination with surgery and radiotherapy. Results from this study suggested that paclitaxel was a feasible agent that could be used in patients who experienced a minimal response to initial FAC, as almost half of such patients treated with paclitaxel were able to undergo mastectomy. A follow-up retrospective review by the authors compared patients treated with FAC + paclitaxel with a historical cohort of patients treated with FAC only and found that those treated with paclitaxel had better median overall survival[44]. Although evidence now supports the use of taxane-containing chemotherapy regimens[45], the evidence for their use during the time period of our study was not clear[34].

Trastuzumab, a new, monoclonal antibody, targets the extracellular domain of the Her-2 neu protein receptor found in some breast tumours[46]. Trastuzumab is now commonly used in Her-2 positive breast cancer; however, a limited number of reports are

available regarding use of this agent in the IBC population. One small study examined the use of trastuzumab in locally advanced breast cancer patients who were treated with docetaxel and subsequent doxorubicin and cyclophosphamide. In this study, 40.9% of patients had IBC. 77.3% of all patients had an objective clinical response and of these, 40.9% showed a complete response[47]. It is also interesting to note that Her-2 over-expression has been reported to occur at a greater rate in patients with IBC compared with non-IBC patients[48].

All breast cancer patients with positive estrogen and/or progesterone receptors are considered candidates for endocrine therapy. Selective estrogen receptor modulators (ex. Tamoxifen) and/or aromatase inhibitors (ex. Letrozole and Anastrozole) are efficacious therapies in the adjuvant setting for early breast cancer[49]. Endocrine therapy may be used as the sole therapy in elderly patients with advanced breast cancer due to the decreased toxicity profile compared to chemotherapy[50, 51]. However, as noted above, IBC tumours are more likely to have negative hormone receptor status.

2.4.4 Current Treatment Guidelines

Similar to non-IBC, modern treatment strategies involve a multimodal approach in which chemotherapy, surgery, radiation therapy and hormonal therapy are employed to varying degrees[34, 52]. The general recommended treatment path first involves neoadjuvant anthracycline-based chemotherapy. Following neoadjuvant chemotherapy, mastectomy plus surgical removal of the axillary nodes (axillary lymph node dissection) is recommended. Following mastectomy, high-dose radiation therapy directed to the

chest wall and axilla is recommended. Patients whose tumours have positive hormone receptors should then receive an endocrine therapy. Additionally, tumours with positive Her2Neu receptors should receive trastuzumab. Although consensus statements for IBC management exist for treating patients in Canada[34] they are relatively new (published in 2004) and controversies remain. These include the optimal sequencing of surgery, radiotherapy, and chemotherapy, the type of local-regional therapy, and the most appropriate combination of chemotherapeutic agents.

These practice guidelines are based on the best available evidence, but are often limited to results from small, retrospective, single-centre studies of IBC patients and few RCTs[34]. A number of limitations are associated with single institution reports, including concerns of referral bias[53] and treatment selection bias[54], which can limit the generalizability of the results. The available RCT evidence is limited to a few small studies that include a heterogeneous mix of locally advanced breast cancers, with only a few cases of IBC. Perloff *et al.* randomized 87 patients, of whom 10 had IBC, to either RT or surgery, which was preceded by neoadjuvant chemotherapy. The results from this study showed that there was no significant difference in disease control or survival between the RT or surgery arm[55].

2.5 Importance of Population-based Research

2.5.1 Role of Population-based Research in Cancer Care

Population-based studies can be used to describe the prevalence/incidence of a clinical problem, to describe variations in the management of a disease, to describe the

outcome of a disease, and to explore associations between variations in practice and variations in outcomes[56]. Population-based studies describe the relationship between an exposure and an outcome where the sample of patients is based on the entire population. By sampling from the entire population, population-based studies are able to overcome referral biases commonly associated with single-centre studies (where the underlying sampling frame is usually unknown) thereby improving the external validity. Population-based studies also include a large sample of cases, which can increase the power to detect statistically significant differences. Methodological techniques can also be employed to minimize the impact of treatment selection bias, including before/after study designs, and the instrumental variables approach (IVA).

2.5.2 Instrumental Variables Approach

The IVA is one tool that can be used to evaluate the effectiveness of treatments using observational study designs, and has its origins in economics research[57-59]. The IVA is often employed in situations where RCTs either have not, or cannot be done due to either feasibility and/or ethical concerns. The IVA attempts to exploit the natural experiments that exist when practice varies. Exploiting natural experiments is a common practice in epidemiological studies. The IVA differs, however, in that it attempts to calculate an estimate of treatment effectiveness based on the variations in outcome and practice.

The IVA defines a variable, the instrument, which meets two important criteria. First, the ideal instrument is one that is directly related to the treatment received, and so

variations in practice are observed across levels of the instrument. Second, the instrument has no direct effect on the outcome of interest. When used in observational studies, the IVA attempts to provide a pseudo-randomization, by utilizing an instrument that meets the above two criteria. In the context of a RCT, the instrument is the randomization process, which completely determines the treatment received, and has no direct affect on outcome. Because of the randomization process, any difference in outcome between the two groups can be attributed to the treatment that was received.

One of the key assumptions of the IVA is that the instrument used is not associated with known or unknown patient and disease characteristics, as these factors will have a direct influence on the outcome. The IVA says that when known characteristics (i.e. those available from your data) do not vary across the instrument that you have selected, then it is unlikely that unknown characteristics (i.e. those not available in your data) will vary across the instrument. By assessing variations in outcome across levels of the instrument and not directly comparing outcomes among treated groups, it is possible to minimize treatment selection-bias and thereby improve the internal validity. Large sample sizes are also needed in order to maximize the precision of the treatment effect estimates.

Stukel *et al.* provide an example of using the IVA to assess treatment effectiveness with respect to the utilization of cardiac catheterization in the treatment of acute myocardial infarctions[54]. The authors used regional variations in cardiac catheterization rates as their instrument, and grouped patients into quintiles based on variations in the rates of utilization. Regional groupings based on the utilization rates

served as a good instrument as it was shown to be highly correlated with the likelihood of receiving the treatment. As well, patients across the levels of the instrument had similar prognostic factors, suggesting that the instrument was unrelated to the outcome of interest (survival). Using this instrument allowed the authors to quantify the effectiveness of treatment for a marginal population of patients, defined as those who would receive catheterization in regions with higher rates, but would not receive catheterization in regions with lower rates. The generalizability of the treatment effectiveness measure is limited however, as the results can only be generalized to this marginal population, and do not apply to the majority of patients who would either always receive cardiac catheterization, or never receive cardiac catheterization.

2.5.3 Examples of Population-based Research

When the levels of evidence for the management of a disease are poor, population-based research is useful in identifying practice variations and controversies in the management of a disease. A classic example of this type of research is found in a study by Wenneberg & Gittelsohn[60]. The researchers reported on variations in the utilization of different surgical procedures across hospital areas of Maine, Rhode Island, and Vermont. This research documented wide variations across geographical areas. One of the driving factors of this variation was controversy related to the most appropriate rate of surgical utilization. For example, procedures for which there was little disagreement in the literature, like inguinal hernia repair, showed very little practice variation across

regions. However, for surgical procedures with limited clinical evidence, the rates of utilization varied greatly.

In the presence of evidence on disease management, population-based research can also describe the adoption of therapies. Work done by Lomas et al. explored the impact of treatment guidelines on the utilization of cesarean deliveries[61]. This study analyzed the rates of cesarean section across hospitals in Ontario before and after the release of national treatment guidelines. Although the researchers found that many physicians were familiar with the guidelines, rates of cesarean had changed very little following their release, which indicated the need for better translation and implementation of guidelines.

Additional work by Lomas explored the role that different influences within a physician's environment can have on physician decision-making, in order to better understand how best to implement practice guidelines[62]. The patient, both as an individual and as represented by advocacy groups, can most directly influence physician decision-making. For example, patients can pressure physicians to incorporate newly publicized research evidence into their clinical management. Administrative policies and the technological capabilities within the practice environment can also influence the adoption of medical practices. Public policy, such as government funding for different treatments, also influences medical practice. As well, peer pressures from colleagues and medical associations can influence medical decisions. This work indicated that a coordinated approach, which takes into account all of the factors that can influence physician decision making, is needed for successful practice guideline implementation.

2.5.4 Examples of Population-based Research in Cancer Care

There are a number of examples of population-based research in cancer care. One study described the adoption of a new treatment option for cervical cancer. The management of cervical cancer had long included the use of surgery and/or radiotherapy. However, following positive findings from RCTs that examined the use of concurrent chemotherapy alongside radiotherapy, treatment guidelines were released recommending that management include use of concurrent chemoradiotherapy[63]. Pearcey *et al*. conducted a population-based study to describe the adoption of concurrent chemoradiotherapy for the management of cervical cancer and to explore changes in survival before and after the release of these treatment guidelines[64]. They found rapid adoption of the new combined modality treatment approach, and observed a corresponding improvement in patient survival. This study was important in that it confirmed that physicians' practice was being guided by positive evidence from the RCTs and demonstrated that the survival improvements in the general population were consistent with outcomes that would be expected based on the RCT results.

Another population-based study exploited natural differences in the management of glottic cancer across geographic regions and described how outcomes varied across the regions[65]. A previous international survey on the patterns of care for glottic cancer had identified disagreement among doctors with respect to the most appropriate management strategy[66]. In general, doctors practicing in the United States were more likely to use surgery over radiotherapy compared to doctors practicing in Canada, which has implications for the patient's ability to maintain their natural voice. There was limited

RCT evidence regarding the management of glottic cancer and practice was largely being driven by single-institutional reports. Groome *et al.* took advantage of the natural difference in management philosophy between the two countries to compare the management and outcome of glottic cancer between patients living in Ontario and the United States. The authors found that there was no apparent survival advantage despite differences in the utilization of surgery compared to conservative management with radiotherapy across the regions.

There is a paucity of data regarding the relationship between management and survival for IBC at the population-based level. The only work is a population-based study, by Panades *et al.*[16] that detailed the management of IBC through a retrospective chart review performed on 308 IBC patients treated with a curative intent identified by the British Columbia Cancer Agency. They observed a 13% increase in 10-year loco regional relapse free survival, which was paralleled by increased utilization of mastectomy in conjunction with chemotherapy and radiotherapy.

2.6 Summary

IBC is a rare form of breast cancer associated with poor outcomes. In Ontario, there is currently no data on the incidence or survival of this disease and no information on how these rates may have changed over time. There is also no data on how IBC patients in Ontario have been managed. The purpose of this thesis was to describe the incidence, outcome, and management of IBC for patients diagnosed in Ontario.

2.7 References

1. Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2008.

2. Cancer Care Ontario. Cancer Fact: Years of life lost to cancer in Ontario April 2007. Available from URL: http://www.cancercare.on.ca/cms/one.aspx?pageId=8651 [accessed May/20, 2009].

3. Wood WC, Muss HB, Solin LJ, Olopade OI. Malignant tumors of the breast. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005: 1415.

4. Bevers TB. Primary prevention of breast cancer, screening for early detection of breast cancer, and diagnostic evaluation of clinical and mammographic breast abnormalities. In: Hunt KK, Robb GL, Strom EA, Ueno NT, eds. *Breast Cancer.* 2nd ed. New York: Springer; 2008: 27 - 55.

5. McTiernan A. Behavioral risk factors in breast cancer: Can risk be modified? *Oncologist*. 2003;8: 326-34.

6. Sprague BL, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Hamptom JM, Newcomb PA. Proportion of invasive breast cancer attributable to risk factors modifiable after menopause. *Am J Epidemiol*. 2008;168: 404-411.

7. Greene FL, Page DL, Fritz A, Balch CM, Haller DG, Morrow M. *AJCC Cancer Staging Manual.* Vol 6th. New York: Springer-Verlag; 2002.

8. Bonnier P, Charpin C, Lejeune C et al. Inflammatory carcinomas of the breast: A clinical, pathological, or a clinical and pathological definition? *Int J Cancer*. 1995;62: 382-385.

9. Bell C. *A System of Operative Surgery Founded on the Basis of Anatomy*. Hartford, CT; 1816.

10. Lee BJ, Tannenbaum EN. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet*. 1924;39: 580-595.

11. Dawood S, Cristofanilli M. What progress have we made in managing inflammatory breast cancer? *Oncology (Williston Park)*. 2007;21: 673-679.

12. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH. Epidemiology of inflammatory breast cancer (IBC). *Breast Disease*. 2005;22: 9-23.

13. Bryant T. *Diseases of the Breast.* London: Cassell; 1887.

14. Percy C, Fritz A, Jack A et al. *International Classification of Diseases for Oncology (ICD-O).* Vol 3rd. World Health Organization; 2000.

15. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology,

and End Results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97: 966-975.

16. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: A population-based survival analysis. *J Clin Oncol*. 2005;23: 1941-1950.

17. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program of the National Cancer Institute, 1975-1992. *Cancer*. 1998;82: 2366-2372.

18. Wingo PA, Jamison PM, Young JL, Gargiullo P. Population-based statistics for women diagnosed with inflammatory breast cancer (United States). *Cancer Cause Control*. 2004;15: 321-328.

19. National Institute of Cancer. *SEER Extent of Disease: 1988 Codes and Coding Instructions.* 3rd ed. ; 1998.

20. Boussen H, Bouzaiene H, Ben HJ, Gamoudi A, Benna F, Rahal K. Inflammatory breast cancer in Tunisia: Reassessment of incidence and clinicopathological features. *Semin Oncol*. 2008;35: 17-24.

21. Gunhan-Bilgen I, Ustun EE, Memis A. Inflammatory breast carcinoma: Mammographic, ultrasonographic, clinical, and pathologic findings in 142 cases. *Radiology*. 2002;223: 829-38.

22. Bonnier P, Romain S, Dilhuydy JM et al. Influence of pregnancy on the outcome of breast cancer: A case-control study. Societe Francaise de Senologie et de Pathologie Mammaire study group. *Int J Cancer*. 1997;72: 720-727.

23. Clegg LX, Reichman ME, Miller BA et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: Selected findings from the surveillance, epidemiology, and end results: National longitudinal mortality study. *Cancer Causes & Control*. 2009;20: 417-435.

24. Merkin SS, Stevenson L, Powe N. Geographic socioeconomic status, race, and advanced-stage breast cancer in New York City. *Am J Public Health*. 2002;92: 64-70.

25. Rutqvist LE, Bern A, Stockholm Breast Cancer Study G. Socioeconomic gradients in clinical stage at presentation and survival among breast cancer patients in the Stockholm area 1977-1997. *International Journal of Cancer*. 2006;119: 1433-1439.

26. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. *J Clin Oncol*. 1998;16: 3731-3735.

27. Kleer CG, van Golen KL, Merajver SD. Molecular biology of breast cancer metastasis. inflammatory breast cancer: Clinical syndrome and molecular determinants. *Breast Cancer Res*. 2000;2: 423-429.

28. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: Population based study. *BMJ*. 2000;320: 474-478.

29. Mackillop WJ, Zhang-Salomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. *J Clin Oncol*. 1997;15: 1680-1689.

30. Boyd C, Zhang-Salomons JY, Groome PA, Mackillop WJ. Associations between community income and cancer survival in Ontario, Canada, and the United States. *Journal of Clinical Oncology*. 1999;17: 2244-2255.

31. Singletary SE. Surgical management of inflammatory breast cancer. *Semin Oncol*. 2008;35: 72-77.

32. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. *Breast Disease*. 2005;22: 67-73.

33. Scarth H, Cantin J, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: Mastectomy or lumpectomy? the choice of operation for clinical stages I and II breast cancer (summary of the 2002 update). *CMAJ*. 2002;167: 154 - 155.

34. Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. treatment for women with stage III or locally advanced breast cancer. *Can Med Assoc J*. 2004;170: 983-994.

35. Woodward WA, Buchholz TA. The role of locoregional therapy in inflammatory breast cancer. *Semin Oncol*. 2008;35: 78-86.

36. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: A review. *J Clin Oncol*. 1992;10: 1014-1024.

37. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. *J Clin Oncol*. 2008;26: 786-790.

38. Kuerer HM, Newman LA, Smith TL et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. 1999;17: 460-469.

39. Tack DK, Palmieri FM, Perez EA. Anthracycline vs nonanthracycline adjuvant therapy for breast cancer. *Oncology (Williston Park)*. 2004;18: 1367-1376.

40. Levine MN, Bramwell VH, Pritchard KI et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *Journal of Clinical Oncology*. 1998;16: 2651-2658.

41. Veyret C, Levy C, Chollet P et al. Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: Ten-year results from the French adjuvant study group GETIS 02 trial. *Cancer*. 2006;107: 2535-2544.

42. Ueno NT, Buzdar AU, Singletary SE et al. Combined-modality treatment of inflammatory breast carcinoma: Twenty years of experience at M. D. Anderson Cancer Center. *Cancer Chemoth Pharm*. 1997;40: 321-329.

43. Cristofanilli M, Buzdar AU, Sneige N et al. Paclitaxel in the multimodality treatment for inflammatory breast carcinoma. *Cancer*. 2001;92: 1775-1782.

44. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, Kau SW, Frye DK, Hortobagyi GN. Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: The M. D. Anderson Cancer Center experience. *Clin Breast Cancer*. 2004;4: 415-419.

45. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database of Systematic Reviews*. 2007: 004421.

46. Carter P, Presta L, Gorman CM et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci U S A*. 1992;89: 4285-4289.

47. Van Pelt AE, Mohsin S, Elledge RM et al. Neoadjuvant trastuzumab and docetaxel in breast cancer: Preliminary results. *Clin Breast Cancer*. 2003;4: 348-353.

48. Turpin E, Bieche I, Bertheau P et al. Increased incidence of ERBB2 overexpression and TP53 mutation in inflammatory breast cancer. *Oncogene*. 2002;21: 7593-7597.

49. Giordano SH. Update on locally advanced breast cancer. *Oncologist*. 2003;8: 521-530.

50. Cheung KL. Endocrine therapy for breast cancer: An overview. *Breast*. 2007;16: 327-343.

51. Mano M, Fraser G, McIlroy P et al. Locally advanced breast cancer in octogenarian women. *Breast Cancer Res Tr*. 2005;89: 81-90.

52. National Comprehensive Cancer Network (NCCN). The NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. [accessed June/18, 2009].

53. Gibbons RJ. Referral bias: A difficult but important topic. *J Nucl Cardiol*. 2004;11: 107-109.

54. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: Effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297: 278 - 285.

55. Perloff M, Lesnick GJ, Korzun A et al. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: A cancer and leukemia group B study. *Journal of Clinical Oncology*. 1988;6: 261-269.

56. Booth CM, Mackillop W.J. Translating new medical therapies into societal benefit: The role of population-based outcome studies. *JAMA*. 2008;300: 2177-2179.

57. Newhouse JP, McClellan M. Econometrics in outcomes research: The use of instrumental variables. *Annu Rev Public Health*. 1998;19: 17-34.

58. Grootendorst P. A review of instrumental variables estimation in the applied health sciences. Available from URL: http://socserv2.socsci.mcmaster.ca/~sedap/p/sedap215.pdf [accessed June/18, 2009].

59. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29: 722-729.

60. Wennberg JE, Gittelsohn A. Variations in medical care among small areas. *Sci Am*. 1982;246: 120-136.

61. Lomas J, Anderson GM, Domnick-Pierre K, Vayda E, Enkin MW, Hannah WJ. Do practice guidelines guide practice? The effect of consensus statement on the practice of physicians. *N Engl J Med*. 1989;321: 1306-1311.

62. Lomas J. Retailing research: Increasing the role of evidence in clinical services for childbirth. *Milbank Q*. 1993;71: 439-475.

63. National Cancer Institute. NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival. Available from URL: http://www.nih.gov/news/pr/feb99/nci-22.htm [accessed August 6, 2009, 2009].

64. Pearcey R, Miao Q, Kong W, Zhang-Salomons J, Mackillop WJ. Impact of adoption of chemoradiotherapy on the outcome of cervical cancer in Ontario: Results of a population-based cohort study. *J Clin Oncol*. 2007;25: 2383-2388.

65. Groome PA, O'Sullivan B, Irish JC et al. Glottic cancer in Ontario, Canada and the SEER areas of the United States: Do different management philosophies produce different outcome profiles? *J Clin Epidemiol*. 2001;54: 301-315.

66. O'Sullivan B, Mackillop WJ, Gilbert R et al. Controversies in the management of laryngeal cancer: Results of an international survey on patterns of care. *Radiother Oncol*. 1994;31: 23-32.

Chapter 3

Manuscript 1

This manuscript is intended for *Cancer* and is written in accordance with their submission guidelines.

Title: The Incidence and Survival of Inflammatory Breast Cancer in Ontario

Running Title: Incidence and Survival of IBC

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Condensed Abstract:

We observed that the incidence of IBC has increased over time and we have confirmed the poor survival for IBC. We observed an improvement in long-term (10-year) survival over time.

Abstract

Background: Inflammatory breast cancer (IBC) is a rare form of breast cancer. We described the incidence and survival of IBC in Ontario and explored temporal variations in survival.

Methods: We conducted a retrospective, population-based, cohort study. We identified all primary, pathologically confirmed female breast cancers in the Ontario Cancer

Registry diagnosed 1984-2005. Pathological IBC cases were identified by the histology code '85303' and linked to Canadian census data and cancer centre records. TNM staging data were available on a small subset registered at a cancer centre within 3 months of diagnosis. Using this subset, we compared the relationship of pathological IBC to clinical T4d (i.e., clinically diagnosed IBC). Age-adjusted incidence rates were calculated. The Kaplan-Meier product-limit method was used to estimate survival and log-rank statistics were used to compare different groups of cases.

Results: 1,034 cases of pathologically confirmed IBC and 122,051 cases of pathologically confirmed non-IBC were identified. Using available staging data we determined that 25/54(46.3%) of T4d cases had pathological IBC and estimate that 1.9% of all breast cancer cases were clinicopathological IBC between 2003-2005. Age-adjusted incidence rates of IBC increased from $0.57/10^5$ women-years in 1984-1987 to $1.15/10^5$ in 2003-2005($p<0.0001$). 10-year survival was 21.5% (95% CI: 18.7–24.5) for IBC cases compared to 61.7% for non-IBC (95% CI: 61.4 – 62.0). For IBC, 10-year survival increased from 12.0% (95% CI: 8.3-16.3) for those diagnosed between 1984-1994 to 24.0% (95% CI: 20.1-28.2) for those diagnosed between 1995–2005.

Conclusions: Rates of IBC have increased over time in Ontario. We confirm the poor outcome for IBC but have observed an improvement in long-term survival.

Key Words: Inflammatory breast cancer, incidence, survival, trends

Introduction

Inflammatory breast cancer (IBC) is a rare form of breast cancer characterized clinically by diffuse erythema and edema of the breast, often without a palpable lump[1]. These clinical changes are thought to result from tumor cells invading the dermal lymphatics of the breast[2].

The UICC (International Union Against Cancer)/AJCC (American Joint Committee on Cancer) considers IBC to be a clinicopathological entity identified by the TNM classification 'T4d'[1]. Alternatively, studies making use of administrative data have defined IBC based on the conservative ICD-O (International Classification of Disease for Oncology) histology code "8530/3" which is used by pathologists to indicate when tumor cells have invaded the dermal lymphatics. Using this conservative definition, it has been reported that between 0.1 and 1.1%[3-6] of all breast cancers are IBC. Although conservative definitions have been used by other studies, defining IBC this way is thought to underestimate rates of total IBC[7]. Risk factors for IBC are not well characterized but IBC is often diagnosed at a younger age and African-American women are more likely to develop IBC than Caucasian women[3-5]. Although the association between race and IBC has been explored, the relationship between other indicators of socio-economic status (SES) and IBC has not been studied. However, it has been shown that lower SES is associated with more advanced breast cancer stage at diagnosis[8]. Patients with IBC are known to have poorer survival rates compared to those with non-IBC[3, 4].

To date there have been no studies that describe the incidence or survival for women with IBC in Ontario, the most populous province in Canada. We sought to describe trends in the incidence and survival of pathologically confirmed IBC for patients diagnosed between 1984 and 2005 using data from the Ontario Cancer Registry. Additionally, we explored temporal variations in survival. We also described the relationship between pathologically confirmed IBC and clinicopathological T4d, using staging data available for a small subset of the population, in order to estimate total IBC.

Methods

Study Design

We conducted a retrospective, population-based, cohort study of the incidence and survival of inflammatory breast cancer (IBC) in Ontario, for cases diagnosed between 1984 and 2005. Ethics approval for this project was obtained from the Queen's University Health Sciences Research Ethics Board.

Sources of Data

We made use of the secure, password-protected data systems held onsite at the Division of Cancer Care and Epidemiology at Queen's University in Kingston, Ontario.

Ontario Cancer Registry. Patients were identified using the Ontario Cancer Registry (OCR), a population-based registry that contains information on all incident cases of cancer in the province. The following pieces of information are available from the OCR: unique patient numeric identifier, cancer diagnosis codes (International

Classification of Disease version 9 [ICD-9]), date of diagnosis, tumor histology (International Classification of Diseases for Oncology [ICD-O][9]), date of birth, vital status (alive or dead), date of death, postal code, and Ministry of Health (MOH) residence code at the time of diagnosis. The operation and design of the OCR has been described previously[10]. In brief, using probabilistic matching the OCR compiles each case of cancer from the following sources: 1) registrations at cancer centers, 2) hospital discharge abstracts received from the Canadian Institutes of Health Information (CIHI), 3) pathology reports received from acute care hospitals, and 4) the underlying cause on death certificates[11]. Each compiled cancer record is assigned a unique numeric identifier. The ability of the OCR to capture incident cases of cancer has been measured using capture-recapture methodologies and is greater than 95% for all sites combined[12].

Cancer Centre Records. Electronic cancer centre records were provided by the eight regional cancer centres and included information on the TNM stage of breast cancer for patients diagnosed between 2003 and 2005, and who were registered at a cancer centre within 3 months of diagnosis.

Canadian Census Data. Statistics Canada provided yearly, age-specific estimates of the female population of Ontario based on mid-interval Canadian census data. As well, a descriptor of socioeconomic status (SES) at the level of census enumeration area and census subdivision was provided.

Data Linkage

The OCR retains the source files allowing the unique numeric identifier to be attached back to the source records. The cancer registration source file also contains the cancer centre chart number, which allowed for electronic cancer centre records to be deterministically linked to the OCR. Ontario female population estimates were linked to each OCR cancer record by year and age at diagnosis. SES was linked to each case in the OCR using postal code or MOH residence codes at the time of diagnosis, as described previously[13].

Data Processing

Adjusted median household income was used as an indicator of SES and was categorized into quintiles with 1 representing the poorest and 5 representing the richest quintile.

Study Population

Using the OCR, we identified all cases of primary, female breast cancers, as indicated by the ICD 9 code '174', diagnosed between 1984 and 2005 in Ontario (n=128,572). Breast cancer cases lacking a histologically confirmed diagnosis were excluded (n=5,487), leaving 123,085 cases of histologically confirmed, female breast cancers. From this population cases of IBC were identified using the ICD-O histology code '8530/3' (n=1,034). We assessed differences in the year and age of diagnosis for those excluded breast cancer cases and found that there was no meaningful change in the

number of cases lacking histologically confirmed disease over time, but that they were more likely to be older (80+ years) at the time of diagnosis. Given that IBC is typically diagnosed at a younger age at diagnosis, there is unlikely to be a major understimation in our identification of IBC cases.

Statistical Analysis

Variations in SES and age at diagnosis were compared between IBC and non-IBC patients using the chi-squared test for categorical variables. Odds ratios were calculated to assess the strength of association of SES between IBC and non-IBC while controlling for age, using logistic regression.

We performed a sensitivity analysis to assess the relationship between pathological IBC and T4d. Staging information was available for a small subset of patients diagnosed between 2003 and 2005 who were registered at a regional cancer centre within 3 months of diagnosis. Using this subset, we identified cases of clinicopathologic IBC (defined by TNM classification 'T4d') and determined the proportion with pathological IBC (defined by the histology code '85303').

The 3-year age-adjusted incidence rate of pathologically confirmed IBC was calculated for the years 1984 to 2005, using the 1991 Canadian female population as the standard[14]. The population at risk was Ontario women aged 20 years and older during each time period, approximated by mid-interval Canadian census data. For comparison, age-adjusted incidence rates of non-IBC were also calculated. Age-specific incidence rates for IBC and non-IBC were also calculated. The Wilcoxon rank-sum test was used

to assess the statistical significance of the difference in median age at diagnosis for IBC and non-IBC patients. Poisson regression was performed to assess the statistical significance of differences in the incidence of IBC over time.

The Kaplan-Meier product-limit[15] method was used to estimate survival from the date of diagnosis to the date of death from any cause. Patients still alive on December 31, 2007 were censored at that point as that is the last date of complete death information. Survival of different groups of cases was compared using log-rank statistics. Cox-proportional hazards regression was used to control for age in the survival comparisons of IBC by time period, with cases being split into two time cohorts based on the year of diagnosis. Our decision to split the data into two time cohorts was to allow for sufficient sample size and power to detect a significant difference.

All statistical analyses are based on a two-tailed significance level of <0.05. All statistical analyses were performed using the SAS System for Windows version 9.1.3.

Results

Table 1 presents the baseline characteristics of all patients diagnosed between 1984 and 2005. Between 1984 and 2005, 1,034 cases of primary, pathologically confirmed IBC and 122,051 cases of primary, pathologically confirmed non-IBC were diagnosed. There was a statistically significant difference in the SES distribution between IBC and non-IBC patients ($p=0.033$), with IBC patients being less likely to live in the highest income neighborhoods compared to non-IBC (Odds ratio adjusted for age: 0.75 [95% CI: 0.62 – 0.92], lowest quintile was reference).

Figure 1 contrasts the age-specific incidence rate for IBC and non-IBC patients. The median age at diagnosis was 54.0 years for IBC patients and 60.0 years for non-IBC patients ($p<0.0001$). The maximum age-specific incidence rate for IBC occurred two decades before the peak age-specific incidence rate for non-IBC.

Figure 2 shows that the age-adjusted incidence rate of IBC doubled from 0.57 cases per 100,000 women years (1984 – 1987) to 1.15 cases per 100,000 women years (2003 – 2005) ($P<0.0001$) while the age-adjusted incidence rate for non-IBC was stable over the same time period (120 cases per 100,000 women years between 1984 - 1987 compared to 126 cases per 100,000 women years between 2003 – 2005).

Using available staging information for a small subset of IBC patients diagnosed between 2003-2005, we assessed the relationship between pathologically confirmed IBC and T4d (Table 2). We determined that 25/54 (46.3%) of T4d cases had pathologically confirmed IBC. Based on a correction factor of 54/25 we estimate that between 2003 and 2005, 1.9% of all breast cancers would have been clinicopathologic IBC. Of the 10 patients with pathologically confirmed IBC not identified as T4d, 70% had TNM classification T4 with no further designation.

Figure 3 displays the survival curves comparing women with IBC and non-IBC (Log rank test, $p<0.0001$). 5-year survival was 34.6% (95% CI: 31.5 – 37.5) for IBC patients and 77.2% (95% CI: 76.9 – 77.4) for non-IBC patients. 10-year survival was 21.5% (95% CI: 18.7 – 24.5) for IBC patients and 61.7% (95% CI: 61.4 – 62.0) for non-

IBC patients. Median survival for women with IBC was 2.9 years (95% CI: 2.72 – 3.26) compared with 14.9 years (95% CI: 14.73 – 15.10) for women with non-IBC.

Figure 4 displays the changes in the survival of IBC patients based on the year of diagnosis (Log rank test, p=0.004). Median survival increased from 2.7 years (95% CI: 2.29 – 3.06) for patients diagnosed between 1984-1994 to 3.1 years (95% CI: 2.78 – 3.71) for patients diagnosed between 1995-2005. There was a slight increase in 5-year survival from 31.7% (95% CI: 26.8 – 36.7) to 35.3% (95% CI: 31.5 – 39.2) for patients diagnosed between 1984 - 1994 and 1995 – 2005, respectively. 10-year survival increased from 12.0% (95% CI: 8.3 – 16.3) to 24.0% (95% CI: 20.1 – 28.2) for patients diagnosed between 1984-1994 and 1995-2005, respectively. Median age at diagnosis differed across the time cohorts, and was controlled for in an adjusted multivariate model. For patients diagnosed in 1984 - 1994 the unadjusted hazard ratio was 1.24 (95% CI: 1.07 – 1.44) and the adjusted hazard ratio was 1.28 (95% CI: 1.11 – 1.49) compared to patients diagnosed in 1995 – 2005 (reference group).

Discussion

Using a conservative pathological definition, we observed that over the whole study period, 0.8% of all histologically confirmed breast cancers were IBC. Other population-based studies, using the same pathological definition of IBC, have observed that between 0.1 and 1.0% of all breast cancer diagnoses were IBC[3-6]. Studies that use a pathological definition of IBC are unable to account for any of the clinical characteristics of IBC and are thought to underestimate the true incidence and proportion of IBC[4]. We

estimate that between 2003 and 2005 1.9% of all breast cancers were clinicopathologic IBC, which is similar to the findings of other population-based studies defining IBC as a clinicopathological entity[4, 7, 16].

Similar to other population-based studies[3, 4, 6], we have found that women with IBC were diagnosed at a younger age than women with non-IBC (median age at diagnosis 54.0 years vs. 60.0, IBC vs. non-IBC, respectively, $p<0.0001$). We found that women who were diagnosed with IBC were less likely to live in the highest income neighborhoods compared to women with non-IBC. Although this was statistically significant, the actual difference in SES distribution between IBC and non-IBC was small. Also, our SES measure is ecological and should be interpreted with caution given that we do not have access to individual-level SES data. As well, our measure of SES does not take into account differences in the cost-of-living across the province.

We have observed an increase in the age-adjusted incidence rate for IBC over time. Between 1984 –1987 and 2003 – 2005, the incidence rate of IBC doubled from 0.57 cases per 100,000 women years to 1.15 cases per 100,000 women years, whereas over the same time period the incidence rates of non-IBC remained stable. Chang et al., using cases identified in the SEER (Surveillance, Epidemiology, and End Results) database, found that between 1975-1977 and 1990 – 1992 the incidence of pathologically-confirmed IBC doubled, from 0.3 to 0.7 cases per 100,000 person years among white women and 0.6 to 1.1 cases per 100,000 person years for African American women[3]. We were unable to verify a difference in incidence by race, as race is not

tracked by the OCR. However our data are consistent with the observation of an increased incidence of IBC over time.

The apparent increase in IBC might be attributed to different factors. The increase is unlikely to be due to changes in the pathological definition of the disease, as the association between dermal lymphatic invasion and IBC has been proposed from as early as 1887[7, 17]. Although we were not able to validate the pathology records, our observed differences in age at diagnosis and survival between pathologically confirmed IBC and non-IBC are similar to those reported in the literature, providing support for our disease definition. It is possible that changes in the management of IBC over time may have affected the number of pathological cases identified. The adoption of neoadjuvant chemotherapy might have resulted in the identification of fewer cases with pathological evidence of IBC at the time of surgery, related to complete or partial responses to chemotherapy. But if this were the case, it would result in an underestimation of the number of pathologically-confirmed cases of IBC. It is unlikely that the increased use of breast cancer screening is an explanation for the increased incidence of IBC. Starting in 1990, the Ontario Breast Screening Program was initiated across the province to ensure all women aged 50 and older had access to regular breast screening mammograms[18]. Mammography is able to detect skin thickening changes related to the dermal lymphatic invasion of tumor cells, but underlying masses are often not detected[19] and mammography is thought to be the least sensitive imaging modality for detecting IBC[20]. As such, the adoption of the screening program is likely to play a limited role in explaining the increased incidence. Finally, changing patterns of suspected IBC risk

factors, namely reproductive hormone exposures and obesity, might explain some of the increase in IBC incidence. A single-centre study by Chang et al.[21] reported that high body mass index (BMI) was strongly and significantly associated with increased IBC risk (Odds ratio 2.45 95% CI (1.05 – 5.73)). Given the concern over increasing BMI among the general population, it is possible that this may have contributed in part to the rise in IBC cases, although additional research is needed to confirm any link between BMI and IBC.

Our results confirm that women with IBC have poorer survival rates compared to women with non-IBC and provide a direct measure of how much worse their survival is. We observed an improvement in median survival over time for IBC patients, equivalent to approximately 5 months. 10-year survival improved significantly, doubling from 12.0% to 24.0%, indicating an improvement in long-term survival. We did not have access to some key prognostic factors like stage at presentation, and hormone receptor status, however, we have no reason to suspect that case-mix might have changed over this time period. We did not explore how variations in management over these time periods might have affected this change in survival, but we plan to explore this further in a subsequent study. We have used overall survival as our measure of outcome, as it is a robust measure. As well, in the context of IBC, we would expect cancer-specific survival rates to be similar to overall survival rates, given the poor prognosis associated with this disease. Chang et al. reported changes in overall survival between 1975-1979 and 1988-1992 and found a significant improvement in 3-year survival, from 32% in 1975-1979 to 42% in 1988-1992 (P=0.02)[3]. Panades et al. found no significant improvement in breast

cancer-specific survival for IBC diagnosed between 1991-2000 and 1980-1990, but did find a significant improvement in loco-regional relapse-free survival[16].

This study was population-based and unlike comparisons of survival from single-centre reports, our study avoids potential referral biases by including the entire population of patients. We have described for the first time the incidence and survival of IBC for the whole of Ontario. We have confirmed that IBC is a rare disease, and that its incidence appears to have increased over time. We have also confirmed the poorer survival for IBC patients compared to non-IBC, but note that improvements in survival for patients with IBC, especially long-term survival, have been made. These data will help further inform health care practitioners of the burden of this disease within the province.

Figures

Figure 1 – The age-specific incidence rate of inflammatory breast cancer (IBC) and non-IBC, diagnosed between 1984 and 2005

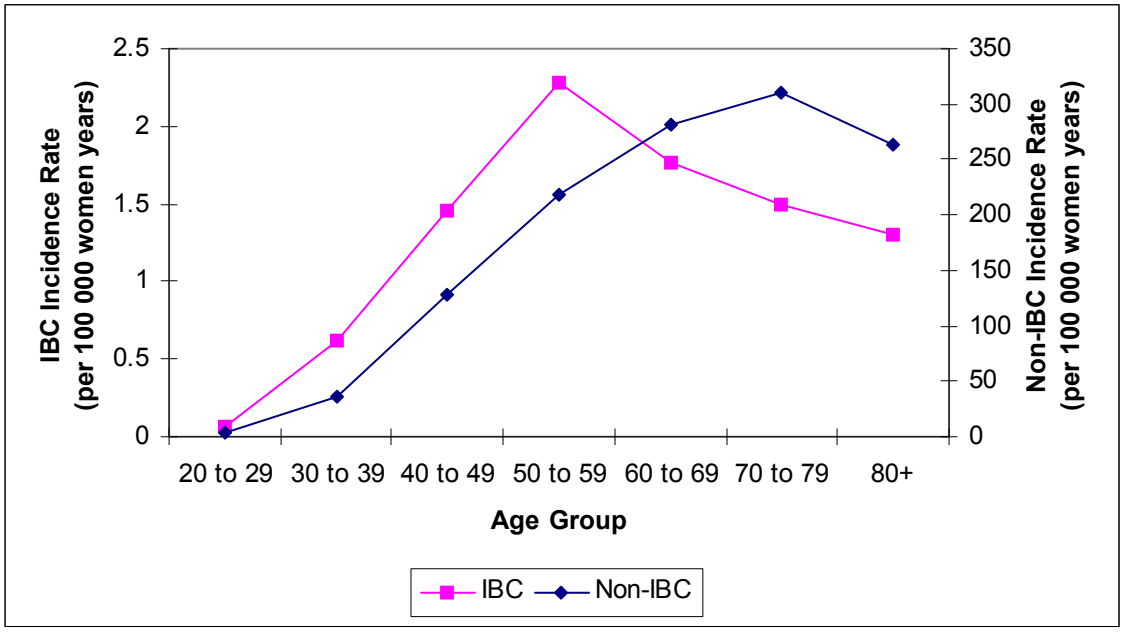


Figure 2 – The age-standardized incidence rate of inflammatory breast cancer (IBC) and non-IBC in Ontario, diagnosed between 1984 and 2005 by 3-year intervals

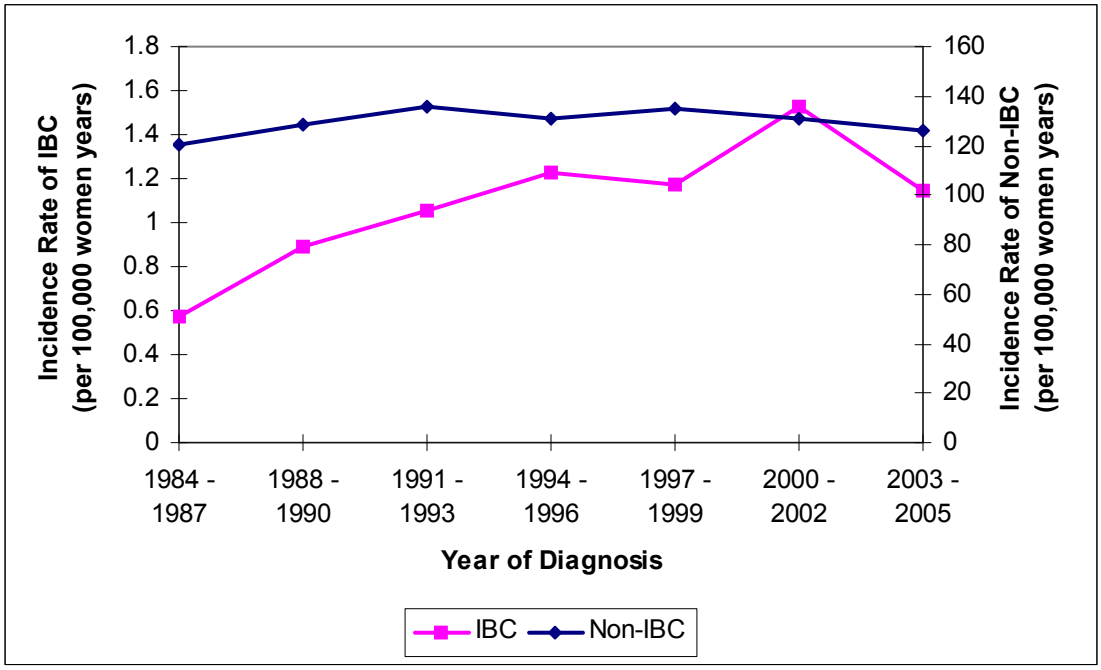


Figure 3 – The overall survival for inflammatory breast cancer (IBC) and non-IBC, diagnosed between 1984 and 2005, p<0.0001

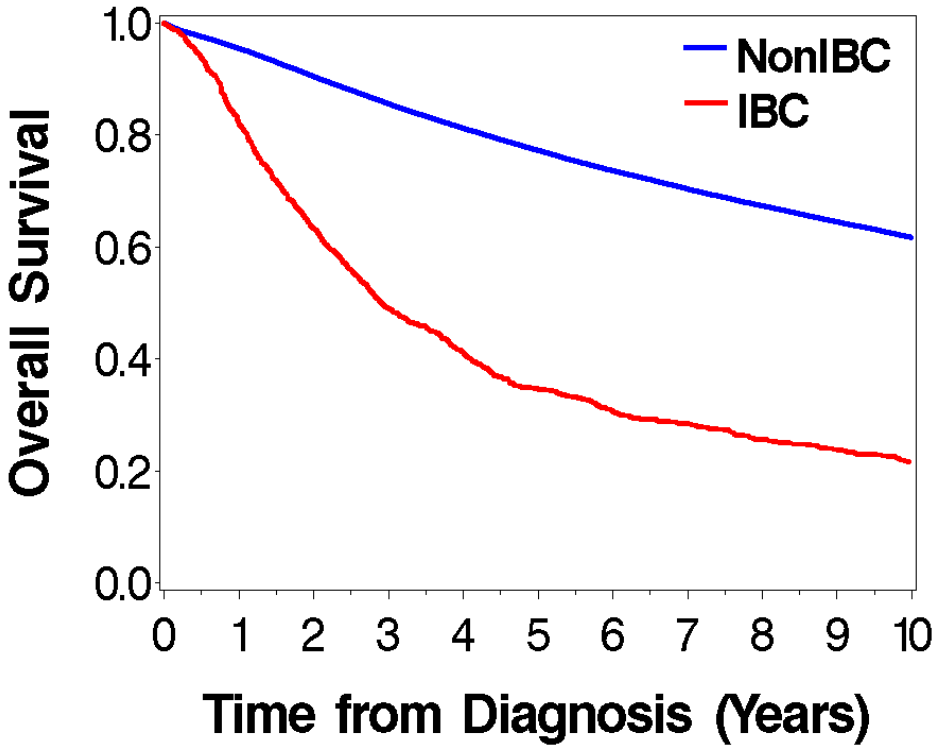
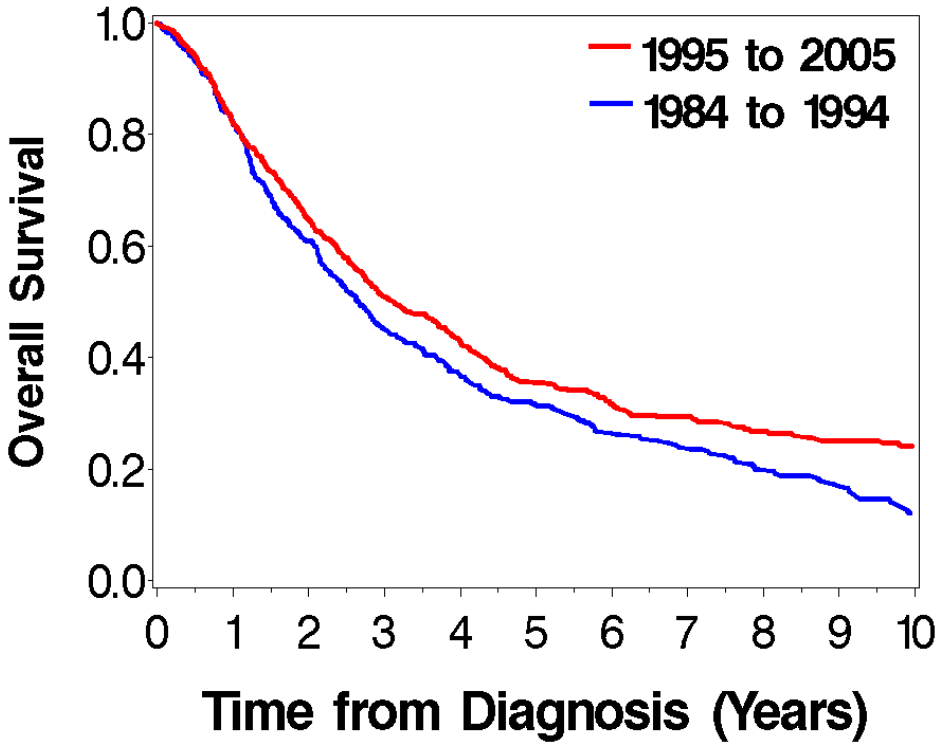


Figure 4 – Changes in the overall survival for patients with inflammatory breast cancer over time, based on the year of diagnosis, p=0.004



Tables

Table 1 – Baseline characteristics of breast cancer patient population, diagnosed 1984 – 2005

Table 1 - Baseline characteristics of breast cancer patient population, diagnosed 1984 - 2005		
	IBC (n=1,034)	**Non-IBC (n=122,051)**
Age group (%)		
<50	37.7	24.9
50-59	28.4	23.0
60-69	17.4	23.5
70-79	10.9	19.2
80+	5.5	9.5
Missing	0.0	0.0
SES (%)		
1 (Poorest)	19.9	19.2
2	23.1	20.1
3	20.7	19.9
4	18.0	19.0
5 (Richest)	17.8	20.9
Missing	0.5	1.0
Note: P-values for chi-square test: Age, p<0.0001; SES, p=0.033		
Abbreviation: SES, socioeconomic status		

Table 2 – Relationship between pathologically confirmed inflammatory breast cancer (IBC) and T4d IBC, diagnosed between 2003 – 2005

Table 2 - Relationship between pathologically confirmed inflammatory breast cancer (IBC) and T4d IBC, diagnosed between 2003 - 2005			
	T4d IBC		
pathIBC*	Yes	No	Total
Yes	25	10	35
No	29	4297	4326
Total	54	4307	4361
Note: *Defined by ICD-O histology code '85303'.			

References

1. Greene FL, Page DL, Fritz A, Balch CM, Haller DG, Morrow M. *AJCC Cancer Staging Manual.* Vol 6th. New York: Springer-Verlag; 2002.

2. Levine PH, Veneroso C. The epidemiology of inflammatory breast cancer. *Semin Oncol*. 2008;35: 11-16.

3. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program of the National Cancer Institute, 1975-1992. *Cancer*. 1998;82: 2366-2372.

4. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97: 966-975.

5. Anderson WF, Chu KC, Chang S, Sherman ME. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2004;13: 1128-1135.

6. Wingo PA, Jamison PM, Young JL, Gargiullo P. Population-based statistics for women diagnosed with inflammatory breast cancer (United States). *Cancer Cause Control*. 2004;15: 321-328.

7. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH. Epidemiology of inflammatory breast cancer (IBC). *Breast Disease*. 2005;22: 9-23.

8. Merkin SS, Stevenson L, Powe N. Geographic socioeconomic status, race, and advanced-stage breast cancer in New York City. *Am J Public Health*. 2002;92: 64-70.

9. Percy C, Fritz A, Jack A et al. *International Classification of Diseases for Oncology (ICD-O).* Vol 3rd. World Health Organization; 2000.

10. Clarke EA, Marrett LD, Kreiger N. Cancer registration in Ontario: A computer approach. In: Jensen OM, Parkin DM, Maclennan R, Muir CS, Skeet RG, et al, eds. *Cancer Registration: Principles and Methods.* Lyons, France: International Agency for Research on Cancer; 1991: 246-257.

11. Paszat LF, Groome PA, Schulze K, Holowaty EJ, Mackillop WJ. A population-based study of the effectiveness of breast conservation for newly diagnosed breast cancer. *Int J Radiat Oncol Biol Phys*. 2000;46: 345-353.

12. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol*. 1988;41: 495-501.

13. Mackillop WJ, Zhang-Salomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. *J Clin Oncol*. 1997;15: 1680-1689.

14. Statistics Canada. 1991 Census of Canada: Profile data.

15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53: 457-481.

16. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: A population-based survival analysis. *J Clin Oncol*. 2005;23: 1941-1950.

17. Bryant T. *Diseases of the Breast.* London: Cassell; 1887.

18. Cancer Care Ontario. Information for Primary Care Providers on the Ontario Breast Screening Program (OBSP). Available from URL: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13806 [accessed June/18, 2009].

19. Chow CK. Imaging in inflammatory breast carcinoma. *Breast Disease*. 2005;22: 45-54.

20. Le-Petross CH, Bidaut L, Yang WT. Evolving role of imaging modalities in inflammatory breast cancer. *Semin Oncol*. 2008;35: 51-63.

21. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. *J Clin Oncol*. 1998;16: 3731-3735.

Chapter 4

Manuscript 2

This manuscript is intended for *Breast Cancer Research and Treatment* and is written in accordance with their submission guidelines.

Title: Exploring Temporal and Regional Variations in the Management of Inflammatory Breast Cancer in Ontario

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Abstract

Purpose: To describe temporal and regional variations in the management of inflammatory breast cancer (IBC) across the province of Ontario, and to explore variations in survival.

Methods: We used a population-based cancer registry to identify 973 cases of pathologically confirmed IBC diagnosed in Ontario, Canada between 1984 and 2004. Electronic records detailing surgical procedures, radiotherapy administration, and chemotherapy administration were linked to the registry. We explored temporal trends in management, based on the year of diagnosis, and explored regional variations in management by stratifying across the nine cancer centres. Chi squared tests were used to assess statistical significance. The Kaplan-Meier product-limit method was used to estimate survival and log-rank statistics were used to compare different groups of cases.

Results: We observed temporal trends that indicated increasing utilization of combination mastectomy and postoperative radiotherapy (28.9% in 1984-1994 compared with 46.1% in 1995-2004, $p<0.0001$). Regardless of radiotherapy use, more patients received mastectomy over time. We observed no statistically significant difference in the utilization of chemotherapy over time. Anthracycline-based combination therapies were the most commonly administered. Across cancer centres, we observed variations in the utilization of combination mastectomy and postoperative radiotherapy ranging from

29.8% (Centre C) to 54.7% (Centre A) ($p<0.0001$). Although not statistically significant, we observed wide differences in overall survival across cancer centres.

Discussion: The management of IBC has shifted over time towards the increased use of mastectomy and postoperative radiotherapy. Additional prognostic information is needed in order to determine how variations in practice may be related to variations in outcome.

Key Words: inflammatory breast cancer, management, radiotherapy, chemotherapy, mastectomy, trends

Introduction

Inflammatory breast cancer (IBC) is a rare form of breast cancer that has very poor survival rates. The management of IBC has evolved over time with the goal of improving patient outcomes. Historically, patients treated with surgery alone had 5-year survival rates of less than 5%[1]. Currently, management strategies involve a multimodal treatment approach in which chemotherapy, endocrine therapy, radiotherapy, and surgery are employed[2, 3]. Chemotherapy is typically administered first in order to shrink the tumour to improve the likelihood of successful surgical removal, and also to treat any clinically undetectable micrometastatic disease[4]. Following neoadjuvant chemotherapy, locoregional treatment including mastectomy and radiotherapy is recommended. Although the adoption of these multimodal strategies has been attributed to an improved outcome the survival remains poor, with one population-based study reporting a median survival of 2.9 years[5].

The levels of evidence for the management of IBC are poor[3], with most reports on IBC management being observational studies performed at individual institutions. A number of limitations are associated with single institution reports, including concerns of referral bias[6] and treatment selection bias[7], which can limit the generalizability of the results. When levels of evidence are poor there is a greater likelihood of variations in the management of the disease, especially when more than one treatment option is available[8, 9]. The instrumental variables approach (IVA) is one method that can be used to assess treatment effectiveness when practice varies[10, 11]. The IVA groups patients with

differing treatment strategies by a variable (the instrument) that is directly related to the practice variation, but not related to the outcome of interest. Comparing available patient and disease characteristics across levels of the instrument is one way to test whether or not the instrument may be associated with the outcome. By assessing survival differences across levels of the instrument, and not directly comparing outcomes among treated groups, it is possible to minimize treatment selection bias.

To date, there have been no studies that describe the management of IBC in Ontario, the most populous province in Canada. We sought to describe temporal and regional variations in the management of IBC across the province of Ontario, for patients diagnosed between 1984 and 2004. Based on the levels of variation in management that we observed, we planned to utilize the IVA to explore aspects of treatment effectiveness. This studies population-based design allows it to be free of referral bias.

Methods

Study Design

We conducted a retrospective, population-based, cohort study on the management of IBC in Ontario, Canada. Ethics approval for this project was obtained from the Queen's University Health Sciences Research Ethics Board.

Sources of Data

We made use of the secure, password-protected data systems held onsite at the Division of Cancer Care and Epidemiology at Queen's University in Kingston, Ontario.

Ontario Cancer Registry. Patients with IBC were identified using the Ontario Cancer Registry (OCR), a population-based registry that contains information on all incident cases of cancer in the province of Ontario. The OCR provided the following information: unique patient group number (used to link data sources), diagnosis codes (International Classification of Disease version 9 [ICD-9]), date of diagnosis, tumour histology (International Classification of Diseases for Oncology [ICD-O]), date of birth, postal code, Ministry of Health (MOH) residence code, vital status (alive or dead), and date of death. The operation and design of the OCR has been described previously[12]. In brief, the OCR compiles cases of cancer by using probabilistic matching of the following sources: 1) registrations at cancer centers, 2) hospital discharge abstracts received from the Canadian Institutes of Health Information (CIHI), 3) pathology reports received from acute care hospitals, and 4) the underlying cause on death certificates. Each compiled cancer record is assigned a unique numeric identifier. The ability of the OCR to capture incident cases of cancer has been measured using capture-recapture methodologies and is greater than 95% for all sites combined[13].

CIHI. The CIHI discharge abstract database provided information on surgical procedures performed across the province. From the CIHI data we obtained the dates of admission (used to represent the date of procedure) and the type of surgical procedure performed.

Cancer Centre Records. Electronic radiotherapy (RT) records were provided by the eight regional cancer centres and the Princess Margaret Hospital (PMH) in Toronto, and are the only providers of RT in Ontario. Each RT record included chart number, start

and end dates of RT treatment, treatment intent, dose and fraction of administered RT, and the anatomic body region(s) irradiated. Previous work has shown that the RT database is more than 95% complete and more than 99% accurate with respect to key variables[14]. Electronic chemotherapy records were provided by the eight regional cancer centres. Each record included chart number, date of administration, and the specific agents administered. Most of these chemotherapy records were captured automatically at the point of prescription, and are therefore of high quality.

Socioeconomic status. Statistics Canada provided descriptors of socioeconomic status (SES) at the level of census enumeration area and census subdivision.

OCR, CIHI, and RT records were available for all patients diagnosed between 1984 and 2004. Chemotherapy records were available for patients treated at a regional cancer centres, diagnosed between 1992 and 2004.

Data Linkage

The OCR retains the source files allowing the unique numeric identifier to be attached back to the source records. The cancer registration source file also contains the cancer centre chart number, which allowed for electronic cancer centre records to be deterministically linked to the OCR. CIHI records were linked to the OCR cancer record using the unique numeric identifier. SES data was linked to each case in the OCR using postal code or MOH residence codes at the time of diagnosis, as described previously[15].

Study Population

Using the OCR, we identified all cases of female, pathologically confirmed IBC diagnosed between 1984 and 2004, based on the ICD-O code '85303'[16] (n=973). Temporal variations in the use of RT and mastectomy were described for these patients, and assessed over two time cohorts based on the year of diagnosis (1984-1994, 1995-2004). This split was made based on previous work that identified changes in outcome over similar time periods[21].

Regional variations in the use of RT and mastectomy were explored for a subset of patients registered at one of the nine cancer centres in the province between 1984 and 2004 (n=885). Variations in survival by cancer centre and by year of diagnosis were also described for these patients. The description of chemotherapy use both over time and by centre was limited to patients diagnosed between 1992 and 2004 and who were treated at one of the seven regional cancer centres that provided chemotherapy data (n=434). Incomplete chemotherapy data was available from the eighth regional cancer centre, and so it was excluded from our description of chemotherapy utilization. For the centre in question, chemotherapy could have been prescribed at one of two hospitals, but prescription records were only available for one of the hospitals.

Data Processing

Median household income was used as an indicator of SES and was categorized into quintiles with 1 representing the poorest and 5 representing the richest using the Ontario general population income distribution. The most responsible cancer centre was

assigned to each case based on the centre where RT and/or chemotherapy were first administered. For those patients with a cancer centre record but no RT or chemotherapy data, the most responsible cancer centre was assigned by using cancer centre registration information provided by the OCR.

We restricted our description of management to treatments received within the first year of diagnosis. This decision was based on the estimated time needed to encompass the administration of multimodal chemotherapy, mastectomy, and RT. Using CIHI data, we identified cases of mastectomy based on the Canadian Classification of Procedures[17] codes: 9712, 9713, 9714 – 9719, 9721 – 9724 (includes codes for complete mastectomy, extended simple mastectomy, radical mastectomy, extended radical mastectomy, and subcutaneous mastectomy).

We identified the first course of RT following the diagnosis of cancer administered with curative intent. Treatment intent was based on the attending radiation oncologist's specifications. For some cases intent was not specified but was assigned based on the dose/fractionation of RT, and the body sites irradiated. Daily dose for each course of RT was calculated by dividing the total administered dose by the total number of fractions. Dose, fraction, and daily dose were categorized based on the distribution of the data. RT administered before surgery was classified as preoperative and RT administered after surgery was classified as postoperative.

We describe the first chemotherapy drug regimens based on the drugs administered within the first month of chemotherapy administration. Regimens were

categorized into three groups: anthracycline-based combination, non-anthracycline-based combination, and single-agent. If chemotherapy administration commenced before surgery it was classified as neoadjuvant and if administration commenced after surgery was classified as adjuvant.

Statistical Analysis

Variations in patient and management characteristics were assessed across time periods and, separately, across cancer centres, using Chi Squared tests (X^2) for categorical variables.

The Kaplan-Meier[18] product-limit method was used to estimate survival from the date of diagnosis to the date of death from any cause, for cases registered at a cancer centre. Patients still alive on December 31, 2007 were censored at that point as that is the last date of complete death information. Survival of different groups of cases was compared using log-rank statistics. Cox-proportional hazards regression was used to control for age in the survival comparison across cancer centres.

All statistical analyses are based on a two-tailed significance level of <0.05. All analyses were performed using the SAS System for Windows version 9.1.3.

Results

There were 973 cases of pathologically confirmed IBC diagnosed between 1984 and 2004. Table 1 displays the patient characteristics. Median age at diagnosis was 54 years (IQR: 45 – 64). Age at diagnosis increased over time (p=0.007). Overall, a greater

proportion of patients fell within the lower SES income quintiles that are set by the general population income distribution. Information on registration at a cancer centre indicates that 91.0% were registered at a cancer centre within the first year of diagnosis.

Mastectomy and Radiotherapy (RT) Utilization

Of the 973 cases of pathological IBC identified, 434 (44.6%) received both mastectomy and RT as part of their management, with 387 (89.2)% of this group receiving postoperative RT. The median time from mastectomy to postoperative RT for this group was 76 days (IQR: 49 – 138). Overall, the median dose of RT administered was 50.0 Gy (gray), the median fraction administered was 25, and the median daily dose was 2.0 Gy per fraction.

Temporal Trends in Mastectomy and RT Utilization

Table 2 presents variations in the order and use of mastectomy and RT over time. Rates of combined mastectomy and RT showed significant temporal variations (Chi square, $p<0.0001$). The proportion of patients to receive combined mastectomy and postoperative RT (indicated by MX + RT) increased from 28.9% for those diagnosed in 1984 – 1994 to 46.1% for those diagnosed in 1995 – 2004. We observed a decrease in the proportion of patients to receive RT without mastectomy over time (23.0% of patients between 1984 – 1994, compared with 9.6% of patients between 1995 – 2004). Utilization of mastectomy (regardless of RT use) increased over time, with 52.1% of patients in 1984 – 1994 receiving mastectomy compared with 69.2% of patients in 1995 –

2004, $p<0.0001$). Total RT dose increased over time ($p<0.0001$) along with increasing number of fractions ($p<0.0001$). There was no temporal change in the median dose, median fractionation, or median daily dose of administered RT.

Variations in Management Across Cancer Centres

Table 3 displays variations in the use of mastectomy and RT for patients registered at one of the nine cancer centres across Ontario ($p<0.0001$). The utilization of combined mastectomy and postoperative RT (indicated by MX + RT) ranged from 29.8% to 54.7% across cancer centres. For all centres, mastectomy and postoperative RT was more common than preoperative RT and mastectomy. Rates of mastectomy use (regardless of RT use) ranged from 46.3% to 76.6% across cancer centres ($p=0.0002$).

Utilization of Chemotherapy

Between 1992 and 2004, 434 patients with IBC were registered at one of seven regional cancer centres across Ontario. Figure 1 shows changes in the use of chemotherapy over time. No statistically significant variation in the utilization of chemotherapy was observed over time ($p=0.17$). Anthracycline-based combination therapies were the most commonly administered. Of those who received anthracycline-based chemotherapy, 52.1% received fluorouracil/epirubicin/cyclophosphamide and 27.6% received fluorouracil/doxorubicin/cyclophosphamide.

Figure 2 shows variations in the utilization of and order of use of chemotherapy, mastectomy, and RT for the management of IBC ($n=434$). The majority (53.5%

[232/434]) received neoadjuvant chemotherapy as their initial treatment. Among this group, 66.8% (155/232) went on to receive mastectomy and 81.9% (127/155) of those that had mastectomy received postoperative radiotherapy.

Overall Survival

Table 4 presents the overall survival for IBC patients who were registered at a cancer centre, stratified by centre and over time. A significant improvement in overall survival was observed over time (log rank, p=0.006), with 10-year survival increasing from 11.9% (95% CI: 8.1-16.5) for patients diagnosed between 1984-1994, to 24.3% (95% CI: 20.2-28.7) for patients diagnosed between 1995-2004. The differences in survival across the nine cancer centres were not statistically significant (log rank, p=0.19). Wide variations in 10-year survival was observed with the estimates between some centres achieving non-overlapping confidence intervals. However, this observation is susceptible to issues of multiple comparisons. We ran multivariate models controlling for age in our by-cancer centre variations in survival and the differences remained non-significant (results not shown).

Discussion

We have described, from a population-based perspective, variations in the utilization of mastectomy, RT, and chemotherapy for the management of pathologically confirmed IBC. Our data show that the management of pathologically confirmed IBC has shifted over time towards the increased utilization of mastectomy. Rates of

mastectomy increased from 52.1% for those diagnosed between 1984–1994 to 69.2% for those diagnosed between 1995– 2004 ($p<0.0001$). Panades *et al.* explored temporal changes in the curative management of IBC for patients diagnosed in British Columbia. They also observed an increased utilization of mastectomy over time, with 32.6% of patients receiving mastectomy for those diagnosed between 1980 – 1985, compared with 78.2% of patients diagnosed between 1996 – 2000[19]. Mastectomy is an important component of local-regional management for IBC, with about 85% of patients who do not undergo surgery developing recurrent disease[20]. We found meaningful and statistically significant improvements in 10-year survival over the same time periods for patients registered at a cancer centre, which is in keeping with previous work[21].

We observed variations in the utilization of mastectomy and RT across cancer centres. Utilization of combination mastectomy and postoperative RT ranged from 29.8% of patients at centre C to 54.7% of patients at centre A ($p<0.0001$). As well, variations in the utilization of mastectomy, regardless of RT, were observed. The variations in practice that we have observed may be due to a number of different factors. Although our study did not detect significant differences in survival across the centres, wide variations were observed. If there are real variations in outcome then regional differences in case-mix, such as stage at presentation, might be related to some of the practice variation. Another factor that might be influencing these variations is differing interpretations of the medical literature, as it was only in the final year of this study that Canadian practice guidelines were published for the management of IBC[3]. It will be interesting to update our management data in the future to determine if and how practice

changes in response to these guidelines, as there is evidence to show that the publication of practice guidelines can[22], but does not always[23], influence practice.

We had planned on using the instrumental variables approach (IVA)[10, 11] to explore aspects of treatment effectiveness, where our instruments were going to be based on temporal and regional variations in multimodal management. However, we were unable to apply this method for a few reasons. Over the entire study period we did observe significant improvements in outcome as well as variations in management with respect to mastectomy and radiotherapy over time. However, we lacked complete chemotherapy information for the full study period, and given the important role that chemotherapy is thought to have played in improving outcomes, exploring treatment effectiveness without this information would not have been very informative. For the subset of cases with chemotherapy, mastectomy, and RT data, no clear natural experiments were observed over time or by region. Additionally, our relatively small sample size would have limited the precision of any treatment effect estimates[10]. Another concern in using the IVA was our limited information on case-mix. Although detailed case-mix information is not necessarily required to perform the IVA, having some information helps to confirm the assumption that the instrument is not associated with outcome. It is normally assumed that if known patient and disease characteristics (i.e. those available in your) do not vary across the levels of the instrument then it is unlikely that unknown characteristics (i.e. those not available in your data) vary, which provides some support that the instrument is not related to the outomce. The validity of this assumption in our data likely would have been limited. For the subset of patients

with complete information on multimodal management, we observed wide heterogeneity in the overall utilization of chemotherapy, mastectomy, and RT (Figure 2). The fact that some cases underwent mastectomy without receiving neoadjuvant chemotherapy strongly suggests that we do not have a homogenous population of patients. As such, had we been able to apply the IVA, any evaluation of treatment effectiveness would have remained susceptible to concerns of treatment selection bias.

While we were unable to directly relate variations in management to outcome, our results provide the first description of how pathological IBC has been managed across Ontario. We have observed temporal changes towards the increased utilization of mastectomy and postoperative RT, which parallels improvements in the long-term outcome of IBC over time. We have also observed that regional variations in the utilization of different management options exist across cancer centres. Future research needs to incorporate detailed prognostic information in order to better assess how differences in case-mix may be influencing the differences in outcome and management observed.

Figures

Figure 1 – Changes in the utilization of chemotherapy for inflammatory breast cancer patients seen at a regional cancer centre (p=0.17).

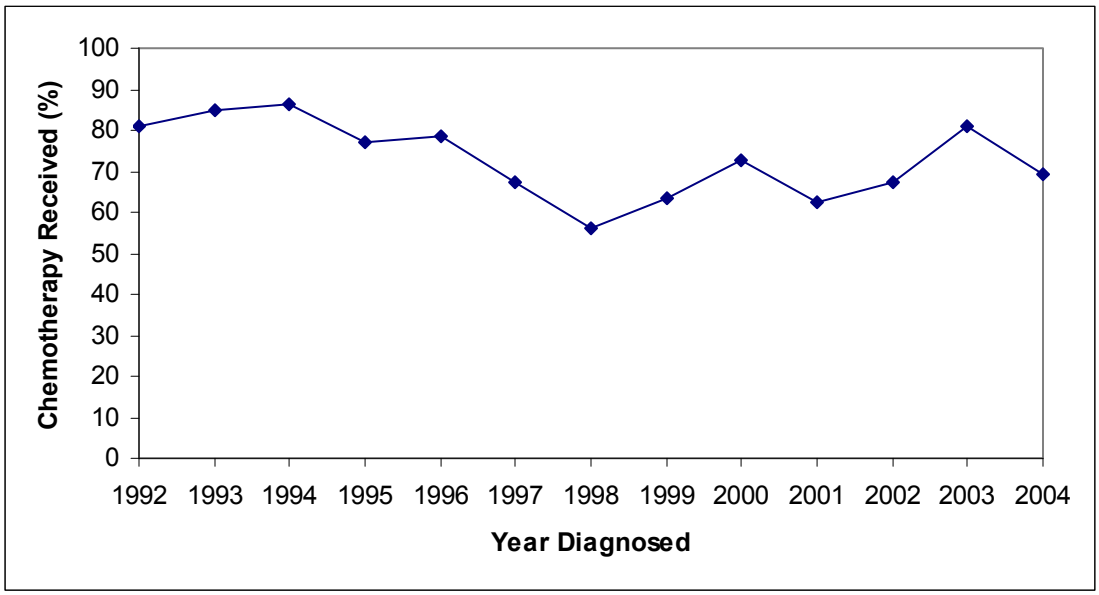
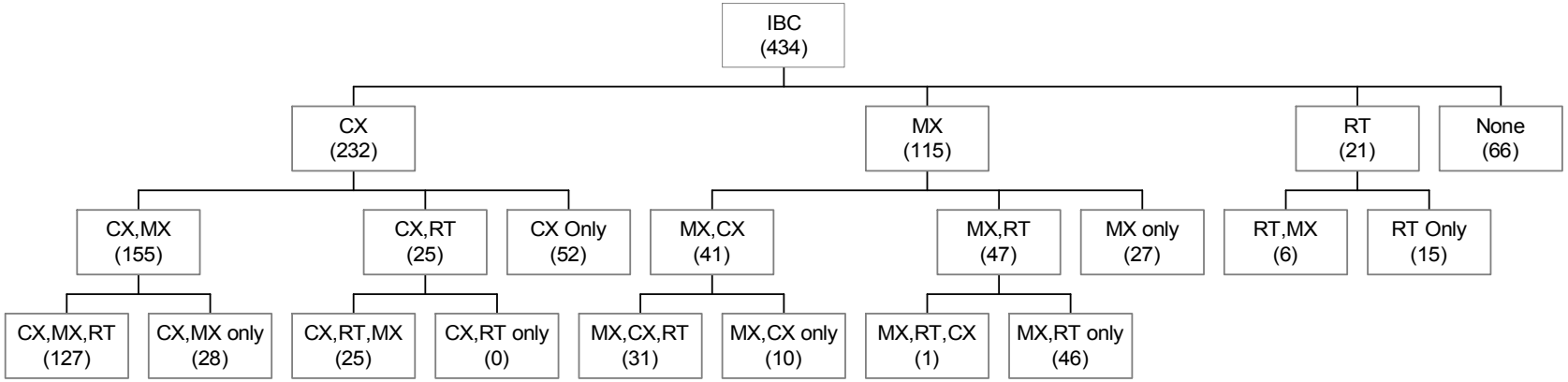


Figure 2 – Variations in the utilization of chemotherapy, radiotherapy, and mastectomy for the management of inflammatory breast cancer patients diagnosed between 1992-2004. Abbreviations: CX – chemotherapy, MX – mastectomy, RT – radiotherapy.



Tables

Table 1 – Characteristics of inflammatory breast cancer patients diagnosed in Ontario between 1984 and 2004

Table 1 - Characteristics of inflammatory breast cancer patients diagnosed in Ontario between 1984 and 2004				
		Year of Diagnosis		
Characteristic	Overall	1984 - 1994	1995 - 2004	P-value
Age (n=973) (%)				
≤39	13.2	17.7	10.6	
40-49	25.1	24.7	25.3	
50-59	28.5	29.1	28.1	
60-69	17.2	16.3	17.7	
70-79	11.0	7.3	13.2	
≥80	5.1	5.0	5.2	0.007
SES, Quintile (n=968) (%)				
1 (Low)	20.5	19.4	21.0	
2	23.2	23.7	23.0	
3	20.5	16.6	22.7	
4	18.2	20.6	16.8	
5 (High)	17.8	19.7	16.5	0.11
Registered at Cancer Centre (n=973) (%)				
Yes	91.0	90.2	91.4	0.53
Note: SES: Socioeconomic status				

Table 2 – Temporal trends in the use of radiotherapy and mastectomy for the management of inflammatory breast cancer between 1984 and 2004

Table 2 – Temporal trends in the use of radiotherapy and mastectomy for the management of inflammatory breast cancer between 1984 and 2004				
	Year of Diagnosis (%)			
Characteristic	Overall	1984 - 1994	1995 - 2004	P-value
Combination Therapy (n=973)				
MX + RT (n=387)	39.8	28.9	46.1	
RT + MX (n=47)	4.8	5.9	4.2	
MX Only (n=178)	18.3	17.4	18.8	
RT Only (n=141)	14.5	23.0	9.6	
Neither MX nor RT (n=220)	22.6	24.9	21.3	<0.0001
Rate of Mastectomy (n=973)				
MX	62.9	52.1	69.2	
No MX	37.1	47.9	30.8	<0.0001
Note: MX: mastectomy, RT: radiotherapy MX + RT – mastectomy followed by postoperative radiotherapy RT + MX – preoperative radiotherapy followed by mastectomy				

Table 3 – Variations in the use of radiotherapy and mastectomy for the management of inflammatory breast cancer across cancer centres between 1984 and 2004.

Table 3 - Variations in the use of radiotherapy and mastectomy for the management of inflammatory breast cancer across cancer centres between 1984 and 2004											
		Cancer Centre (%)									
Characteristic	Overall	A	B	C	D	E	F	G	H	I	p-value
Combination Therapy (n=885)											
MX + RT (n=387)	43.7	54.7	30.5	29.8	47.8	45.5	47.5	40.8	32.5	46.0	
RT + MX (n=47)	5.3	0.5	8.5	4.8	16.2	0.0	3.8	4.1	5.2	4.7	
MX Only (n=137)	15.5	14.8	7.3	23.1	12.6	18.2	13.8	6.1	20.8	18.9	
RT Only (n=141)	15.9	9.9	26.8	22.1	12.6	27.3	11.3	30.6	16.9	13.5	
Neither MX nor RT (n=173)	19.6	20.2	26.8	20.2	10.8	9.1	23.8	18.4	24.7	16.9	<0.0001
Rate of Mastectomy (n=885)											
MX	64.5	70.0	46.3	57.7	76.6	63.6	65.0	51.0	58.4	69.6	
No MX	35.5	30.0	53.7	42.3	23.4	36.4	35.0	49.0	41.6	30.4	0.0002
Note: MX: mastectomy, RT: radiotherapy MX + RT – mastectomy followed by postoperative radiotherapy RT + MX – preoperative radiotherapy followed by mastectomy											

Table 4 – Survival differences for inflammatory breast cancer patients, diagnosed 1984 – 2004.

Table 4 - Survival differences for inflammatory breast cancer patients, diagnosed 1984 - 2004			
Characteristic	Median (years) (95% CI)	5-year (%) (95% CI)	10-year (%) (95% CI)
Overall	2.8 (2.6 - 3.1)	33.8 (30.7 - 37.0)	21.2(18.2 - 24.3)
Cancer Centre			
A	2.7 (2.2 - 3.5)	35.3 (29.1 - 41.7)	26.6 (20.6 - 33.0)
B	2.6 (1.8 - 3.3)	27.7 (18.2 - 37.9)	16.3 (8.7 - 26.0)
C	3.7 (2.4 - 5.0)	40.4 (30.7 - 49.8)	23.9 (15.7 - 33.2)
D	3.3 (2.7 - 4.2)	37.3 (28.2 - 46.4)	20.0 (12.3 - 29.2)
E	2.2 (0.7 - 8.8)	45.5 (16.7 - 70.7)	22.7 (3.8 - 51.1)
F	2.5 (1.9 - 3.6)	28.5 (18.8 - 38.9)	17.6 (10.0 - 27.4)
G	3.3 (2.2 - 5.7)	37.9 (24.2 - 51.5)	27.1 (14.8 - 41.0)
H	2.6 (2.2 - 2.9)	19.8 (11.5 - 29.8)	7.6 (2.4 - 17.0)
I	2.8 (2.2 - 4.0)	35.4 (27.6 - 43.3)	21.9 (14.4 - 30.5)
Year of Diagnosis			
1984 - 1994	2.6 (2.3 - 3.0)	31.2 (26.1 - 36.4)	11.9 (8.1 - 16.5)
1995 - 2004	2.9 (2.6 - 3.6)	34.9 (30.8 - 39.0)	24.3 (20.2 - 28.7)
Note: P-values for log rank test: cancer centre, p=0.19; year of diagnosis, p=0.006. CI: Confidence interval			

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References

1. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. *Breast Disease*. 2005;22: 67-73.

2. National Comprehensive Cancer Network (NCCN). The NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. [accessed June/18, 2009].

3. Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *Can Med Assoc J*. 2004;170: 983-994.

4. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. *J Clin Oncol*. 2008;26: 786-790.

5. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97: 966-975.

6. Gibbons RJ. Referral bias: A difficult but important topic. *J Nucl Cardiol*. 2004;11: 107-109.

7. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: Effects of invasive

cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297: 278 - 285.

8. Wennberg JE, Gittelsohn A. Variations in medical care among small areas. *Sci Am*. 1982;246: 120-136.

9. Chassin MR, Brook RH, Park RE et al. Variations in the use of medical and surgical services by the Medicare population. *N Engl J Med*. 1986;314: 285-290.

10. Grootendorst P. A review of instrumental variables estimation in the applied health sciences. Available from URL: http://socserv2.socsci.mcmaster.ca/~sedap/p/sedap215.pdf [accessed June/18, 2009].

11. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29: 722-729.

12. Clarke EA, Marrett LD, Kreiger N. Cancer registration in Ontario: A computer approach. In: Jensen OM, Parkin DM, Maclennan R, Muir CS, Skeet RG, et al, eds. *Cancer Registration: Principles and Methods.* Lyons, France: International Agency for Research on Cancer; 1991: 246-257.

13. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol*. 1988;41: 495-501.

14. Kong W, Zhang-Salomons J, Hanna TP, Mackillop WJ. A population-based study of the fractionation of palliative radiotherapy for bone metastasis in Ontario. *Int J Radiat Oncol Biol Phys*. 2007;69: 1209-1217.

15. Mackillop WJ, Zhang-Salomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. *J Clin Oncol*. 1997;15: 1680-1689.

16. Percy C, Fritz A, Jack A et al. *International Classification of Diseases for Oncology (ICD-O).* Vol 3rd. World Health Organization; 2000.

17. Statistics Canada - Health Division - Nosology Reference Section. *Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures*. Ottawa: Statistics Canada; 1986.

18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53: 457-481.

19. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: A population-based survival analysis. *J Clin Oncol*. 2005;23: 1941-1950.

20. Veyret C, Levy C, Chollet P et al. Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: Ten-year results from the French adjuvant study group GETIS 02 trial. *Cancer*. 2006;107: 2535-2544.

21. Fralick J, Groome PA, Parulekar W, Mackillop WJ. The incidence and survival of inflammatory breast cancer in Ontario (unpublished). 2009.

22. Pearcey R, Miao Q, Kong W, Zhang-Salomons J, Mackillop WJ. Impact of adoption of chemoradiotherapy on the outcome of cervical cancer in Ontario: Results of a population-based cohort study. *J Clin Oncol*. 2007;25: 2383-2388.

23. Lomas J, Anderson GM, Domnick-Pierre K, Vayda E, Enkin MW, Hannah WJ. Do practice guidelines guide practice? The effect of consensus statement on the practice of physicians. *N Engl J Med*. 1989;321: 1306-1311.

Chapter 5
General Discussion

5.1 Summary of Study Design

Using a retrospective, population-based cohort study, we have described for the first time the incidence, survival, and management of IBC in Ontario. We made use of electronic data sources held onsite at the Division of Cancer Care and Epidemiology at Queen's University, Kingston.

5.2 Overview of Key Findings

The purpose of manuscript 1 was to describe the incidence and survival for women with IBC in Ontario. There were a number of key findings including: 1) an increase in the incidence of IBC over time, 2) women with IBC were diagnosed at younger age than women with non-IBC, 3) women with IBC had a poorer survival compared to non-IBC, and 4) an improvement in the overall survival for women with IBC over time.

We observed that over the entire study period 0.8% of all breast cancers were pathologically confirmed cases of IBC. We were able to estimate that between 2003-2005, approximately 2.0% of all breast cancers were IBC when one considers both the clinical and pathological features of the disease. The incidence of IBC doubled between 1984-1987 and 2003-2005, from 0.57 cases per 100 000 women years to 1.15 cases per 100 000 women years, respectively. Both our observed proportion of breast cancer patients with IBC and our observed increase in incidence is in keeping with existing

population-based literature[1-5]. This increase may be related in part to changing risk factor profiles thought to be associated with this disease, but additional research is needed to determine why this increase has occurred.

In keeping with existing IBC research, we observed that women with IBC were diagnosed at a younger age than women with non-IBC. The median age at diagnosis was 54 years for IBC patients, compared with 60 years for non-IBC patients. With respect to SES, we observed that women with IBC were less likely to live in the highest income neighborhoods compared to women with non-IBC.

We observed a 10-year survival of 21.5% (95% CI: 18.7 – 24.5) for IBC cases compared with 61.7% (95% CI: 61.4 – 62.0) for non-IBC cases ($p<0.0001$, log-rank test), which emphasizes the poor prognosis for IBC patients. There was a statistically significant increase in the long-term survival of IBC patients over time. Between 1984-1994 and 1995-2005, 10-year survival increased from 12.0% (95% CI: 8.3–16.3) to 24.0% (95% CI: 20.1–28.2).

The purpose of our second manuscript was to explore how management varied across the province of Ontario, both temporally and regionally. Manuscript 2 documented a number of key findings including: 1) increased utilization of combination mastectomy and adjuvant RT, and increased mastectomy use over time, 2) differences in the utilization rates of combination mastectomy and RT across cancer centres, 3) large variations in the multimodal use of mastectomy, radiotherapy, and surgery, and 4) wide differences in survival estimates across cancer centres.

The proportion of patients to receive combined mastectomy and adjuvant RT increased from 28.9% for those diagnosed in 1984 – 1994 to 46.1% for those diagnosed in 1995 – 2004. There was also an increase in the use of mastectomy (regardless of radiotherapy use), with 52.1% of patients receiving mastectomy in 1984-1994 compared with 69.2% of patients in 1995-2004. There was no significant change in the utilization of chemotherapy over time.

We observed statistically significant variations in the utilization of mastectomy and RT across cancer centres, with rates of combined mastectomy and adjuvant RT ranging from 29.8% (Centre C) to 54.7% (Centre A) ($p<0.0001$). Rates of mastectomy use (regardless of RT use) ranged from 46.3% to 76.6% across cancer centres ($p=0.0002$). We also explored survival differences across the nine cancer centres. Although wide differences in some of the point estimates of survival were observed, no significant differences between the survival curves were observed across the nine centres (log rank $p=0.19$).

We observed wide variations in the order and use of chemotherapy, radiotherapy, and mastectomy, which was likely related to differing extents of disease at presentation among the IBC cases. As described in manuscript 2, we were unable to conduct an analysis of treatment effectiveness. This was primarily due to our inability to clearly identify a natural experiment to study, which thus prevented application of the instrumental variables approach.

5.3 Study Limitations

A few limitations of this work need to be described. We made use of the OCR, a data source designed for cancer surveillance and not clinical research. While we were able to obtain some important information on IBC management through linkage with the OCRs source files, we were unable to obtain additional clinically-relevant information on risk factors and prognostic factors. Race, an important risk factor known to influence the rates of incidence and age at diagnosis, is not tracked by any of the data sources that we had available to us. As such, we were unable to stratify our results, and explore by-race difference in disease incidence and age at diagnosis, which have been reported in the literature[1]. We also lacked important prognostic information including: complete staging information at the time of diagnosis (i.e. node and distant metastatic disease status), information on tumour responsiveness to chemotherapy, and information on tumour receptor status. Our analysis of management was conducted on an unselected population of patients, some of whom are likely to have presented with metastatic disease at diagnosis. As a result, treatment approaches may have differed given the presence of metastatic disease at the time of diagnosis, and this may partially explain the variations that we observed in the utilization of multimodal therapy. The response of IBC tumours to chemotherapy (i.e. does the tumour shrink in response to chemotherapy administration) is an important prognostic factor[6-8]. As well, tumour receptor status (i.e. hormone receptor status and Her2Neu status) plays an important role in treatment decision-making.

We did not have complete information on chemotherapy or endocrine therapy that may have been administered. We were only able to describe the first round of chemotherapy that patients received, based on the drug regimens received within the first month of treatment. As well, there was no information on chemotherapy administered between 1984 – 1991 and no information on chemotherapy administered in the community or at Princess Margaret Hospital. Additionally, there was incomplete data available from one of the regional cancer centres and as a result, this centre was excluded from our description of chemotherapy utilization. Also, we were unable to describe the utilization of endocrine therapy, as this was not tracked by any of the data sources that we used.

Another limitation of our research pertains to our case definition. Our population was defined based on pathological evidence of dermal lymphatic invasion, and did not account for the clinical features of IBC. We were able to assess the relationship between pathologically confirmed IBC and clinical T4d IBC in a small subset of patients for whom staging data was available, and confirm that using a pathological definition underestimates the total proportion of IBC. Also, we did not have access to the pathology records to verify the accuracy of the diagnosis of dermal lymphatic invasion. However, our findings of 1) a younger age at diagnosis, and 2) the obvious difference in survival between IBC and non-IBC patients are consistent with the literature and provide support for our disease definition.

Finally, although we detected wide differences in the estimates of survival across cancer centres in manuscript 2, we were unable to detect a statistically significant

difference. Post-hoc sample-size calculations were performed to determine the number of cases that would have been needed to observe a statistically significant difference in survival between two centres, and these results indicate that we would have needed 185 cases from each centre to detect a significant difference in survival at 10-years. For the two centres for which the sample-size calculation was based on, we had a combined 296 cases. We also assessed the post-hoc power of our study to detect 1) a difference in survival over time and 2) variations in aspects of management over time, and confirm that our study was sufficiently powered to detect statistically significant differences. Results for the power and sample size calculations can be found in the supplemental results appendix.

5.4 Strengths of Study

The greatest strength of this study comes from its population-based design. We have included all IBC cases diagnosed in the province, allowing for a large cohort of a considerably rare disease. Our estimates of survival were based on the entire population of IBC patients and as such, our study was able to avoid potential referral bias commonly associated with single-institutional reports[9].

Another strength was our ability to assess the relationship between pathologically confirmed IBC and clinical IBC in a small subset of patients. We can confirm that pathological definitions of IBC tend to underestimate the proportion of total IBC, as found by previous research[10].

5.5 Implications and Future Research

Data on the incidence of IBC indicates that the number of new cases of IBC has been increasing over time, whereas the number of new cases of non-IBC has remained stable. This increase is likely related to changes in the risk factors associated with this disease but additional epidemiological work is required to understand and characterize the etiology of IBC. As a result of the increasing incidence, health care practitioners are more likely to see cases of IBC in their practices. Family and emergency physicians should familiarize themselves with the unique characteristics of IBC as these physicians play an important role in assuring a timely diagnosis and subsequent referral to oncology specialists to begin management[11].

We have observed improvements in the long-term outcome of IBC over time, which likely reflect more intensive treatment approaches in the management of this devastating disease. The relationship between variations in survival and variations in management, both across time periods and over regions, need to be explored further. Additional information on prognostic factors will aid in assessing how differences in case-mix may be influencing the differences in outcome and management observed. In the meantime, oncologists should continue to manage this disease in line with existing, agreed upon practice guidelines[12].

IBC remains a highly fatal disease in comparison to non-IBC, and further research is needed to determine the most effective treatment strategy these patients. Although the gold standard study design is a randomized controlled trial, there are obvious feasibility concerns due to the rarity of this disease. Concerns with feasibility could be

overcome, however, through the organization of coordinated, multi-centre clinical trials. A collaborative effort involving all cancer centres in Ontario could also allow for the creation of a database that collects data specific to patients with IBC. Some Ontario cancer centres have begun to collect data on and follow a prospective cohort of women with locally advanced breast cancer, which includes those with IBC[13]. Prospectively collected data, with detailed patient history, prognostic information, and treatment data will be useful in assessing the link between survival and management and also in exploring factors that might be driving the observed increase in IBC incidence.

To conclude, our research provides health care practitioners with important information on the burden of IBC, and will help to continue and perhaps renew interest in this rare, but fatal disease.

5.6 References

1. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97: 966-975.

2. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program of the National Cancer Institute, 1975-1992. *Cancer*. 1998;82: 2366-2372.

3. Anderson WF, Chu KC, Chang S, Sherman ME. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2004;13: 1128-1135.

4. Wingo PA, Jamison PM, Young JL, Gargiullo P. Population-based statistics for women diagnosed with inflammatory breast cancer (United States). *Cancer Cause Control*. 2004;15: 321-328.

5. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: A population-based survival analysis. *J Clin Oncol*. 2005;23: 1941-1950.

6. Cristofanilli M, Buzdar AU, Sneige N et al. Paclitaxel in the multimodality treatment for inflammatory breast carcinoma. *Cancer*. 2001;92: 1775-1782.

7. Harris EE, Schultz D, Bertsch H, Fox K, Glick J, Solin LJ. Ten-year outcome after combined modality therapy for inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 2003;55: 1200-1208.

8. Ueno NT, Buzdar AU, Singletary SE et al. Combined-modality treatment of inflammatory breast carcinoma: Twenty years of experience at M. D. Anderson Cancer Center. *Cancer Chemoth Pharm*. 1997;40: 321-329.

9. Gibbons RJ. Referral bias: A difficult but important topic. *J Nucl Cardiol*. 2004;11: 107-109.

10. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH. Epidemiology of inflammatory breast cancer (IBC). *Breast Disease*. 2005;22: 9-23.

11. Molckovsky A, Fitzgerald B, Freedman O, Heisey R, Clemons M. Approach to inflammatory breast cancer. *Can Fam Physician*. 2009;55: 25-31.

12. Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *Can Med Assoc J*. 2004;170: 983-994.

13. Fitzgerald B. Moving Towards a Program of Excellence. Available from URL: http://www.petermunkcardiaccentre.ca/Clinics_&_Services/services/LABC/LABC_meeting/presentations/S2_2_Fitzgerald.pdf [accessed June/01, 2009].

Chapter 6
Appendix: Supplemental Results

6.1 Estimation of Study Power and Sample Size

We estimate the post-hoc power of our study to 1) detect a significant improvement in survival over time, and 2) detect a significant difference in practice over time. All power and sample size calculations were performed using the equations found in Fundamentals of Biostatistics by Bernard Rosner[1].

To determine our ability to detect a statistically significant improvement in survival over the two time periods (1984 – 1994, 1995 – 2005), we used the equation for power for the comparison of survival curves between two groups under the Cox Proportional-Hazards Model (Equation 14.47). The probability of failure at 10-years was given by our product-limit estimates, and the relative risk was determined from our Cox-proportional hazards model, comparing survival between IBC cases diagnosed in 1984 – 1994 (group 1) and IBC cases diagnosed in 1995 – 2005 (group 2). Based on 88.02% failing at 10-years in group1 (p_1) and 75.88% failing at 10-years in group 2 (p_2), and a relative risk of 1.28 (reference = group2), we estimate that we had 93.94% power to detect a statistically significant difference in survival at the 0.05 level.

To determine our ability to detect a statistically significant difference in the utilization of mastectomy over two time periods, we used the equation for power achieved in comparing two binomial proportions (Equation 10.15), and based our parameter estimates on the results from Table 2 of Manuscript 2. Group 1 (n_1=317)

corresponded to IBC cases diagnosed between 1984 – 1994, and group 2 (n_2=616) corresponded to IBC cases diagnosed between 1995 – 2004. Based on 52.1% of cases in group 1 receiving mastectomy (p_1), and 69.2% of cases in group 2 receiving mastectomy (p_2), we estimate that we had 99.91% power to detect a statistical difference at the 0.05 level.

We were unable to detect a statistically significant difference in survival across all nine cancer centres as shown by Table 4 in Manuscript 2. We were interested in determining the number of patients that would have been needed to detect a statistically significant difference. The nine levels of our data (corresponding to the nine cancer centres) complicates this sample size calculation, and in order to simplify it, we determine the sample size needed to detect a statistical difference in survival between two cancer centres, based on the survival data from centre A and H (Equation 14.48). Cox-proportional hazards regression between centre A and H was conducted, and the hazard ratio was found to be 0.724 (centre H was reference). Based on the product-limit estimates that were used to derive the survival estimates for table 4, failure at 10-years was 0.7337 (p_A) for those registered at centre A, and 0.9236 (p_H) for those registered at centre H. Based on these parameters, we estimate that we would need 185 cases from each centre to achieve 80% power, with a significance level of 0.05. With that said, the number of cases recruited should be larger to account for the concern of multiple comparisons in choosing to compare survival between only these two centres.

6.2 Comparing Breast Cancer Cases With Versus Without Histologically Confirmed Disease

In Manuscript 1 we excluded breast cancer cases that did not have histologically confirmed disease (n=5,472). In order to determine whether our results might be biased by this exclusion, we compared the year of diagnosis, and age at diagnosis between the two groups (Table A1).

Table 6.1 – Comparing breast cancer cases with versus without histologically confirmed disease, diagnosed 1984 - 2005

Table 6.1 - Comparing breast cases with and without histologically confirmed disease, diagnosed 1984 - 2005

	Histology (n=123,048)	No Histology (n=5,472)
Year of Diagnosis (%)		
1984 - 1994	95.42	4.58
1995 - 2005	95.98	4.02
Age at Diagnosis (%)		
<50	24.98	9.85
50 - 59	23.01	10.82
60 - 69	23.46	15.19
70 - 79	19.09	22.33
80+	9.46	41.81

As seen in Table A1, there were approximately 0.5% more cases without histologically confirmed disease in the early time period compared to the most recent time period. It is unlikely that such a small change between the two time periods would

have biased our temporal results. We do note, however, that those lacking histologically confirmed disease were older compared to those with histologically confirmed disease.

We also explored survival differences between these two groups and found that those cases without histologically confirmed breast cancer had a poorer outcome, with a median survival of 1.5 years (95 % CI: 1.3 – 1.8) compared with 14.7 years (95% CI: 14.5 – 14.8) for all cases with histologically confirmed disease. As well, those cases without histologically confirmed disease had 5-year and 10-year survival rates of 38.4% (37.1 – 40.0) and 30.6% (29.3 – 31.9), respectively. This suggests that women without histologically confirmed disease likely presented with advanced stage breast cancer. It is possible that some of these advanced cases could have been undiagnosed IBC, and so by excluding them from our study, we might be underestimating the total proportion of IBC cases, and our survival estimates may be biased. The magnitude of the underestimation, and the impact on our survival estimates, however, is likely small. This is because over 40% of those cases lacking histologically confirmed disease were 80 years and older. Had we instead observed the worse survival for those without histologically confirmed disease and also found that they were more likely to be younger at diagnosis then there would have been a greater concern that we might have been excluding IBC cases, given that IBC cases are typically diagnosed at a younger age.

References:

1. Rosner B. *Fundamentals of Biostatistics.* 6th ed. USA: Thomson Brooks/Cole; 2006.