ASSOCIATION BETWEEN USE OF A SPECIALIZED DIAGNOSTIC ASSESSMENT UNIT AND THE DIAGNOSTIC INTERVAL IN ONTARIO BREAST CANCER PATIENTS

by

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Abstract

Background: The amount of time that it takes to get a breast cancer diagnosis is very important to patients. The Ontario diagnostic assessment unit (DAU) is designed to improve the quality and timeliness of care during a breast cancer diagnosis. This study described and examined the association between the length of the diagnostic interval and DAU use in Ontario, Canada.

Methods: This was a retrospective cohort study among all breast cancer patients diagnosed between Jan 1st, 2011 and Dec 31st, 2011 in Ontario, Canada. DAU use and diagnostic intervals were described. The association between DAU use and the diagnostic interval was examined separately in a cohort of 2499 screen-detected patients and a cohort of 4381 symptomatic patients. Study data sources included administrative databases available at the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario (CCO). The diagnostic interval was defined as the time from the index contact to the cancer diagnosis. DAU use was determined based on the payment record within the organized screening program as well as the hospital where patients were diagnosed. Multivariate median regressions were used to control for possible confounders.

Results: On average, Ontario breast cancer patients waited 4.6 weeks to be diagnosed. Forty-eight percent were diagnosed in a DAU and 52% were diagnosed in the usual care route. In screen-detected patients, DAUs had a higher rate in meeting national timeliness targets compared to usual care (79.1% vs. 70.2%, $p<0.001$). DAU use was significantly associated with an 8.3-day decrease in the time to diagnosis (95% CI: 6.5-10.2) after controlling for potential confounders. In symptomatic patients, DAUs also had a higher rate in achieving the Canadian timeliness targets compare to usual care (71.7% vs. 58.1%, $p<0.001$). DAUs significantly reduced the time to diagnosis by 10 days (95% CI: 7.8-11.9) after controlling for possible confounders.

Conclusions: We observed considerable variation in breast cancer diagnostic intervals and DAU use in Ontario. Use of Ontario DAUs was associated with improved diagnostic timeliness for breast cancer patients.

Co-Authorship

The thesis is the work of Li Jiang in collaboration with her supervisors Dr. Patti A. Groome and Dr. Julie Gilbert. This thesis is designed by Li Jiang, Dr. Patti A. Groome, and Dr. Julie Gilbert. Insight and expert opinion were provided by Dr. Hugh Langley. Data linkages were performed by Ms. Marlo Whitehead at the Institute for Clinical Evaluative Sciences (ICES). Data preparation and statistical analyses were performed by Li Jiang with suggestions and guidance from Dr. Patti A. Groome. The thesis was written by Li Jiang, with comments and editorial input from Dr. Patti A. Groome and Dr. Julie Gilbert.

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List of Abbreviations

ADG	the Johns Hopkins Aggregated Diagnosis Groups
AJCC	American Joint Committee on Cancer
BAA	Breast Assessment Affiliate
CAPE	Client Agency Program Enrolment
CAR–MAP	Canadian Association of Radiologists – Mammography Accreditation Program
CCI	Canadian Classification for Health Intervention
CCO	Cancer Care Ontario
CNB	Core Needle Biopsy
CIHI/DAD	The Canadian Institution for Health Information Discharge Abstract Database
CSD	Census Subdivision
DA	Dissemination Area
DAU	Diagnostic Assessment Units
ED	Emergency Department
FNAB	Fine Needle Aspiration Biopsy
FP	Family Physician
GP	General Practitioner
HER-2	Human Epidermal Growth Factors Receptor 2
IBC	Inflammatory Breast Cancer
ICD-9	International Classification of Diseases Diagnosis Codes - Version 9
ICD-10-CA	International Classification of Diseases and Related Health Problems, 10th Revision, Canada
ICES	Institute for Clinical Evaluative Sciences
IKN	ICES Key Number
IPDB	ICES Physician Database
MOHLTC	Ontario Ministry of Health and Long-Term Care
MRI	Magnetic Resonance Imaging
NACRS	National Ambulatory Care Reporting System
OBSP	Ontario Breast Screening Program
OCR	Ontario Cancer Registry
OHIP	Ontario Health Insurance Plan Claims Database
OMA	Ontario Medical Association

PAH	Polycyclic Aromatic Hydrocarbons
RIO2008	Rurality Index for Ontario 2008
RPDB	Registered Persons Database
SDS	Same-day Surgery Database
SES	Socio-economic Status
TNM	Tumor-Node-Metastasis
UC	Usual Care
UPC	Usual Provider of Care
WHO	World Health Organization

Chapter 1

Introduction

1.1 Background and Rationale

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths in Ontario women (18;19), accounting for 27% of newly diagnosed cancer cases and 16% of cancer deaths (18). The diagnostic period in breast cancer is characterized by multiple appointments for diagnostic tests and consultations and it often provokes considerable distress and anxiety for women and their families (20-22). A delayed diagnosis is also associated with an advanced cancer stage, more aggressive treatment and a poorer prognosis (23).

In Ontario, efforts to achieve timely diagnosis have led to the development of the diagnostic assessment unit (DAU), which is an organizational structure designed to improve the patient experience and quality of care during a breast cancer diagnosis (24-26). Ontario DAUs are comprised of the breast assessment affiliates (BAA) under the auspices of the Ontario Breast Screening Program (OBSP), and breast assessment centres/programs that were independently developed. DAUs provide centralized and coordinated care within a multidisciplinary environment. A patient navigator at a DAU is responsible for arranging diagnostic investigations and providing patient support. DAUs also ensure the high quality of diagnostic services by applying professional standards and meeting the Ontario Breast Screening Program (OBSP) threshold criteria that are required to maintain the DAU status (26;27).

The literature contains little evidence on the population-level influence of Ontario DAUs on the timeliness of breast cancer diagnosis. The only evidence consists of one retrospective study which suggested that BAAs are more successful in achieving timeliness targets than usual care for patients within the Ontario Breast Screening Program (OBSP) (28). However, we do not know how much quicker the DAU diagnostic process is compared to usual

care at a provincial level for breast cancer patients. We also do not know what proportion of breast cancer patients are diagnosed through DAUs and whether their coverage is population-based in the regions serviced by them. In addition, we do not know the patterns and the length of the diagnostic interval at the provincial level. Therefore, we need to address these knowledge gaps to provide evidence for future program planning.

1.2 Study Design Overview

We conducted a retrospective cohort study among all breast cancer patients diagnosed between Jan 1st, 2011 and Dec 31st, 2011 in Ontario, Canada. The association between DAU use and breast cancer diagnostic interval was examined separately in a cohort of 2499 screen-detected patients and a cohort of 4381 symptomatic patients. Study data were obtained from administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) Queen's Health Services Research Facility, and the Collaborative Stage data and the most recent Ontario Cancer Registry and Ontario Breast Screening Program data were requested from Cancer Care Ontario (CCO). All the databases except for geo-coded information were linked at an individual level using an anonymous ICES Key Number (IKN).

1.3 Study Objectives

The purpose of this study was to describe and compare diagnostic intervals for breast cancer patients diagnosed through a diagnostic assessment unit (DAU) versus those diagnosed through usual care (UC) in Ontario. This study also aimed to provide information on DAU use as well as the length of the diagnostic interval for breast cancer patients in Ontario. Specifically, this study had three objectives:

1. To describe the length of the diagnostic interval and DAU coverage at a provincial level, and also describe their geographic variation by county;
2. To examine the association between DAU use and the diagnostic interval in breast cancer patients whose disease was detected by screening;

3. To examine the association between DAU use and the diagnostic interval in symptomatic breast cancer patients.

1.4 Thesis Outline

This thesis is organized into seven chapters. Chapter 2 presents a review of the literature covering the current knowledge about breast cancer, the diagnostic interval in breast cancer, Ontario diagnostic assessment units, the diagnostic care conceptual framework, and factors associated with the length of the diagnostic interval. Chapter 3 provides detailed information about the study methods, including the study design, study population, data sources, study variables and statistical analysis strategies. Chapter 4 is a manuscript presenting descriptive results of the first study objective, providing information on the length of the breast cancer diagnostic interval and DAU use in Ontario. Chapter 5 contains the second manuscript that presents findings of the association between Ontario DAU use and the length of the diagnostic interval in breast cancer patients whose disease was detected by screening. Chapter 6 is the third manuscript that presents findings of the population-level influence of Ontario DAUs on the diagnostic timeliness in symptomatic breast cancer patients. Chapter 7 is the general discussion, including the summary and discussion of study findings, post-hoc power calculation, study strengths and limitations, and study contributions to the current literature and public health implications.

Chapter 2

Literature Review

2.1 Breast Cancer

2.1.1 Biology and Classification

Breast cancer includes all malignancies that originate from the breast tissue, including ducts and lobules. Breast ducts are composed of an inner layer of luminal epithelial cells responsible for the milk production and an outer layer of myoepithelial cells that have contractile functions (37;38). The branching of breast ducts divides a breast into approximately 15 to 20 lobes, comprising of lobules that are formed by the terminal branch of breast ducts (40). Breast lobules, also known as terminal ductal lobular units (TDLU), are considered the basic functional units of the breast (37).

Breast cancer arising from different cell origins can have very different histopathological features and clinical behaviours (38;41) and can be classified into several breast cancer subtypes (38;46-49). According to the World Health Organization (WHO), there are at least 17 distinct histological types of breast cancer (50). The majority (60%-80%) of breast cancers are classified as invasive ductal carcinoma- not otherwise specified, and the remaining 20% to 40% are breast cancer special types, such as tubular carcinoma, mucinous carcinoma and invasive lobular carcinoma (41). At the molecular level, breast cancer can be classified into five subtypes distinguished by different gene and protein expressions. Two hormone-receptor positive subtypes are luminal A and luminal B, and three hormone-receptor negative subtypes include human epidermal growth factors receptor 2 (HER-2), basal-like and normal breast-like (41;46;47;49). Breast cancer molecular subtypes have been associated with tumor progression and thus have been widely used in the clinical setting to predict cancer prognoses and guide treatment options (46;48).

One distinct clinical presentation of breast cancer is the inflammatory breast cancer (IBC). The American Joint Committee on Cancer (AJCC) defines IBC as a clinicopathologic entity with its diagnosis relying on the clinical but not necessarily pathologic features (51). Inflammatory breast cancer is characterized by the clinical appearance of inflammation with diffuse edema and erythema of the breast, often without an underlying palpable mass (52;53). The clinical appearance of IBC has been attributed to the pathologic plugging of the dermal lymphatics of the breast with tumor emboli (52). Although an aggressive and lethal form of breast cancer, IBC accounts for only 1.9% of all breast cancer cases in Ontario (54).

2.1.2 Descriptive Epidemiology

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths in Ontario women (18;19), accounting for 27% of newly diagnosed cancer cases and 16% of cancer deaths (18). Age-standardized breast cancer incidence and mortality rates in Ontario are 96 and 19 per 100,000 respectively, which translates to estimates of 9,100 new cases and 2,000 deaths in 2012 (19). Incidence and mortality rates of breast cancer are higher among older age groups, with over half of breast cancer found in women aged 50 to 69 (55). The Ontario age-standardized breast cancer incidence rose from 1983 through the early 1990s and stayed stable over the past two decades. In contrast, the age-standardized breast cancer mortality rate declined by 38% over the same time especially for women aged 50 to 69 (19;55). This decrease in breast cancer mortality has been attributed to both the improved breast cancer treatment and the increased participation in breast cancer screening (55).

2.1.3 Risk Factors

There are a number of factors associated with an increased risk of breast cancer. Age is the most important risk factor for breast cancer. Approximately 80% of breast cancer occurs in females aged 50 and older (56) and the chance of getting breast cancer increases rapidly with age (55;57). A family history of breast cancer (58-60), a history of benign breast disease of a specific

high-risk type (e.g. atypical ductal hyperplasia, lobular carcinoma in situ) (58;59), having dense breasts on mammogram (60), an exposure to ionizing radiation early in life (55) or an occupational exposure to carcinogens and endocrine disruptors (61), are also important factors associated with substantial increases in the risk of breast cancer (55;60). Recent studies using genetic profiling technology have identified the BRCA1 and BRCA2 genes as strong genetic risk factors for breast cancer at young ages (40;62). Both the BRCA1 and BRCA2 genes play central roles in DNA repair pathways (46;63) and they account for approximately 30% to 70% of all hereditary breast cancer (62). In two studies, germline mutations in the BRCA1 or BRCA2 were associated with at least an 80% increase in the lifetime risk of breast cancer (62;64).

Most other established risk factors, while important at a population level, are associated with modest elevations in the risk of breast cancer and are largely non-modifiable (65;66). Many are reproductive or hormone-related factors. Early menarche and late menopause have been shown to increase the lifetime risk of breast cancer, both leading to greater lifetime exposure of a woman to estrogen and progesterone (57;62). Biological parity, early full-term pregnancy and longer duration of lactation have been associated with decreased breast cancer risk (55;67). Other reported reproductive and hormone-related factors include the number of miscarriages (55;58), interval between the first and second childbearing, menstrual irregularity (59), and exposure to oral contraceptive pills (59).

Recently, there has been a growing interest in studying environmental risk factors of breast cancer, as evidence suggests that known hereditary or reproductive risk factors explain only 25% to 50% of all breast cancer cases (66;68). Environmental risk factors most frequently examined and associated with breast cancer are nutritional/behaviour risk factors, such as body mass index (57;58), smoking (69), alcohol consumption (70-72), physical activity (73) and preventive health behaviour (58). A recent area of particular research interest is the association between breast cancer and exposure to certain chemicals either in the workplace (61;74) or in

everyday life (75). Identified breast cancer carcinogens include Benzene, polycyclic aromatic hydrocarbons (PAHs), Tetrachlorethylene, heavy metals, pesticides and solvents, according to the International Agency for Cancer Research (76;77) and National Toxicology Program in the United States (78). Apart from these factors, evidence has also suggested that shift work ("light at night") (79;80) and socio-economic status (81) are possibly related to breast cancer risk.

2.1.4 Early Detection

Despite the ongoing research on breast cancer prevention (82;83), an important strategy for breast cancer control is early detection and treatment. Breast cancer patients detected at early stages are more likely to have better clinical outcomes than those detected at late stages. Relative five-year survival for breast cancer patients diagnosed at stage I (98%) and stage II (89%) are much higher than those diagnosed at stage III (60%) and stage IV (28%) (84). Early detection provides more treatment options and a higher chance of survival for cancer patients because the earlier the cancer is detected, the less likely it is to have metastasized (55).

Breast screening is one of the most important strategies to achieve the goal of early detection. International evidence from randomized controlled trials has shown that early detection and treatment through screening can effectively reduce breast cancer mortality by 35% (55;85;86). In particular, there is evidence quantifying the benefits of screening for women aged 50 to 69 (85). As a result, the Ontario Breast Screening Program (OBSP) was launched in 1990 with the aim of reducing mortality from breast cancer (55).

The OBSP is a province-wide, organized breast screening program that provides biennial breast screening services for women aged 50 and older (55). Although the OBSP specifically targets Ontarian women aged 50 to 69, the program has strict eligibility criteria. Women within the age group are only eligible if they 1) have no acute breast symptoms 2) have no personal history of breast cancer 3) have no current breast implant 4) have not had a mammogram within the last 11 months (87). Eligible women can receive a two-view mammography at designated

OBSP site in urban areas or through mobile coaches in remote areas (88). The quality of service is ensured as the program requires affiliated screening sites to provide mammography that meets both OBSP's standards and those of the Canadian Association of Radiologists – Mammography Accreditation Program (CAR–MAP) (89). Once a screening abnormality is detected, both the woman and her physician are informed of the result and further diagnostic work-up is either arranged by the physician or by the OBSP screening centre (90).

Recently, women at high risk of breast cancer (aged 30 to 69) have been given access to screening as part of the Ontario Breast Screening Program. This program expansion was based on the clinical evidence and reviews as well as recommendations from Cancer Care Ontario (91;92). Currently, there are at least 28 high risk screening centres across the province (93). A woman is considered at high risk if she 1) carries deleterious gene mutations (e.g. BRCA1, BRCA2) 2) is the first-degree relative of a mutation carrier and has declined genetic testing 3) has a family history of hereditary breast cancer syndrome and an estimated personal lifetime cancer risk greater than 25% or 4) received chest radiation for treatment of other conditions before the age of 30 and at least 8 years previously (87). Women without these specified high-risk conditions but consider themselves as high risk can be referred to the OBSP genetic assessments and subsequently have their high-risk status determined (92). Since magnetic resonance imaging (MRI) in addition to mammography is the most effective approach for screening women at high risk (91), the OBSP High Risk Screening program offers both MRI and mammography for a woman confirmed as high risk if she has a referral from her physician and has no acute breast symptoms (87).

An alternative to the organized screening program is screening in the public fee-for-service sector, which is also known as the opportunistic screening. Approximately one third of eligible women were screened outside of the OBSP program during 2007 and 2008, according to the statistics from Cancer Care Ontario (55). As there are no mechanisms of targeted population

recruitment, abnormal screening follow-up and quality assurance for opportunistic screening, women are encouraged to receive screening tests from the OBSP (89). The proportion of women within the 50-69 age group who received an opportunistic screening test declined from 37.9% in 2001-2002 to 24.6% in 2007-2008 as more women switched to and benefited from the OBSP (55).

2.1.5 Signs/Symptoms

More than 50% of breast cancer patients in Ontario are diagnosed with signs or symptoms (28;55;94). The majority of breast cancers are first noticed by patients as a lump in the breast, often without pain (44;95). In a small proportion of patients, pain in the breast has been reported as the first symptom (96). Other less common symptoms include thickening and swelling of the breast, skin dimpling or edema, skin irritation or distortion in shape (40;95;97). Nipple symptoms such as spontaneous discharge, retraction, erosion, inversion or tenderness, may also occur (40). As many of these symptoms are also commonly observed in benign breast diseases, the predictive value of symptoms for diagnosing breast cancer is limited (98) and further diagnostic investigations are often needed.

2.1.6 Diagnostic Investigations

Detection of an abnormality in the breast often triggers further diagnostic work-up to confirm or rule out a diagnosis of cancer. The diagnostic pathway can vary depending on patient characteristics and disease presentation (99;100). Diagnostic investigations often include mammography, ultrasound, magnetic resonance imaging (MRI), fine needle aspiration biopsy, core needle biopsy, and open surgery (101).

A diagnostic work-up typically begins with diagnostic imaging, including mammography and ultrasound of the breast, and sometimes magnetic resonance imaging (MRI) (102). In contrast to mammograms done for breast cancer screening in women who have no clinical signs or symptoms, diagnostic mammograms evaluate an abnormal clinical finding in the breast or they further investigate an area of concern from an abnormal screening mammogram (103). Although

a mammogram is the most commonly used initial diagnostic modality, its ability to detect breast cancer decreases with increased breast tissue density (91), which is more common in premenopausal women (91). Other alternatives such as ultrasound and MRI of the breast directed at the area of concern may be preferred, as the dense breast tissue lowers the accuracy of standard mammography (103). MRI of the breast is also used to assess the possibility of BRCA-related breast cancer, the axillary lymph node status with known occult cancer, and the possibility of multiple tumors (102). Overall, diagnostic imaging can rule out some false-positive cases and save patients from invasive diagnostic investigations. In situations where a cancer suspicion remains, further biopsy is often performed to ascertain the nature of the breast abnormality.

Biopsy is the only definitive method for diagnosing breast cancer. Three different types of biopsy can be adopted: fine needle aspiration biopsy, core needle biopsy and open surgical biopsy, with the choice depending on the clinical features of disease, physician's interpretation of previous diagnostic imaging results as well as the availability of resources (101). It is generally recommended in practice that patients should have a tissue biopsy before an open surgery (103).

Fine needle aspiration biopsy (FNAB) is often performed by a radiologist using a thin, hollow needle to obtain a small sample of the cellular tissue from the area of concern (101). FNAB has a reported false negative rate of 1% to 35% and an overall sensitivity of 94% (103). Accuracy relies on the expertise and experience of both pathologists and clinicians who obtain the tissue (101). Core needle biopsy (CNB) is similar to FNAB but uses a wider needle to remove larger and multiple samples of the tissue. CNB is generally considered more accurate than FNAB, with a false negative rate ranging from 1.6% to 19% and an overall sensitivity of 89% (103). Sometimes, vacuum is added to assist traditional CNB, allowing for twice the amount of breast tissue to be removed. In situations where there is a non-palpable mass or lesions are difficult to locate, imaging guidance with mammography, ultrasound or MRI is used to assist in sampling of tissue for both types of tissue biopsies (101).

Surgical biopsy has been considered the criterion for diagnosing breast cancer, and is generally used for an abnormality that is not accessible by a needle biopsy. An incisional biopsy removes a small proportion of lesion while an excisional biopsy removes the entire lesion along with surrounding tissues (101). Sometimes, a preoperative wire location technique is used to guide the direction when there is no palpable lesion or the lesion is difficult to locate (101). Based on biopsy results, a final pathologic diagnosis of breast cancer is made according to the WHO classification and the tumor-node-metastasis (TNM) classification system (102).

The complexity of the breast cancer diagnostic pathway has led to wide variation across Canada in waiting times that lead up to diagnosis (104). The median time to diagnosis following abnormal screening tests ranged from 6.0 to 9.6 weeks for those with a biopsy and 2.9 to 4.3 weeks without a biopsy, according to a report of provincially organized breast screening programs in 1996 (104). Notably, 10% of patients with breast cancer waited 12 weeks or longer to receive a cancer diagnosis (104). These findings have raised concerns about the suboptimal transition from an abnormal screening test to the cancer diagnosis, which could essentially diminish the benefits of cancer screening (88;104;105). While effort needs to continue to enhance breast cancer screening participation, it is also important to minimize the diagnostic interval for resolving abnormal screening tests and diagnosing symptomatic breast cancer.

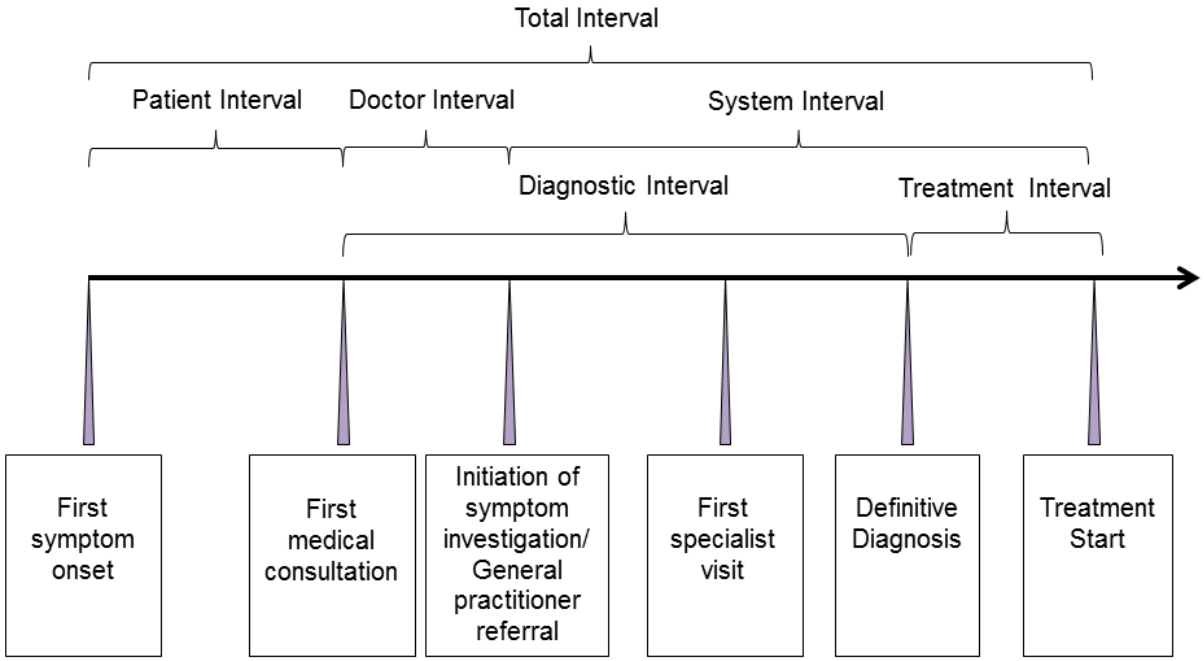
2.2 Diagnostic Intervals in Breast Cancer

2.2.1 Definition

The literature contains different terms to represent the concept of the time that is needed to reach a definitive diagnosis, such as “time to diagnosis” (39), “diagnostic delay” (4;11;13;29;30;42), “follow-up on screening abnormality” (7;106) and “diagnostic interval” (8;107), and the same term is often used differently across studies. Depending on the study population, “diagnostic interval” can either refer to “time from the abnormal screening to the completion of follow-up procedures” among the screening population (107) or “time from the

first examination to the medical diagnosis" among both screen-detected and symptomatic breast cancer patients (8). The terminology is further complicated because the diagnostic interval is often divided into distinct sub-intervals based on key events that distinguish attributors of the delay on the diagnostic pathway. As shown in Figure 2-1, time from abnormality detection to cancer treatment is usually disaggregated into patient interval, doctor interval and system interval (12;108-110). Patient interval refers to the period from the first symptom onset to the first medical consultation, and doctor interval represents the period from the first medical consultation to the initiation of symptom investigation or the practitioner referral. By definition, patients whose cancer was detected through screening tests bypass the patient interval. System interval can be defined as the time interval between the initiation of symptom investigation or the practitioner referral and the start of cancer treatment. Sometimes, doctor interval and system interval are combined as diagnostic interval (8;13). Inconsistencies in terminologies and definitions have created confusion and barriers to comparing results across studies, and there have been some discussions around the appropriate terminology for describing the time needed to reach a diagnosis (111). The conventional terminology used by the majority of literature is “diagnostic delay” (4;11;13;29;30;42). However, some attributed a strong negative connotation to the term “diagnostic delay” (112) and Scott and Walter (111) have suggested alternative terms such as “time to diagnosis” or “intervals” to replace “delay”. We chose to use the term “diagnostic interval” to represent the time studied in this thesis, based on the Aarhus statement developed by an international Consensus Working Group (110) that aims to set standard definitions in the area of early cancer diagnosis.

Figure 2-1: Disaggregation of the breast cancer diagnostic interval



The operational definition of diagnostic interval varies in the literature. Although there is consensus that diagnostic interval terminates at the definitive 'diagnosis', the key point to measure the date of diagnosis varies. Some define the date of 'diagnosis' as the date of first pathologic diagnosis (8;9;13;30;35;45), others measure the date of 'diagnosis' using the date of medical diagnosis (42), date of diagnosis in the cancer registry (33), date of the final diagnostic procedure (11), or date of the diagnostic resolution for abnormal screening tests (7;34). As we used the Ontario Cancer Registry (OCR) to ascertain the date of diagnosis, we defined 'diagnosis' using the priority order listed in the OCR: 1) date of first histology or cytology confirmation of malignancy 2) date of admission to hospital, or date of the first outpatient consultation (113). The starting point for the diagnostic interval differs depending on the disease presentation. In screen-detected cases, the diagnostic interval usually starts from the date of an abnormal screen test (4;9;32;36). In symptomatic cases, the starting point for the diagnostic interval could be the date of the first symptom onset (42), date of the first medical consultation/initial clinic visit (13;30;44)

or date of the first breast specific procedure (8;11). As the aim of this study was to evaluate an organizational structure's influence on the breast cancer diagnostic interval, we defined diagnostic interval as starting from the earliest time that the health care system is informed of an abnormality. This event was defined as the 'index contact' in accordance with one previous study of the diagnostic interval in colorectal cancer (114). We subsequently defined diagnostic interval as the time duration between the 'index contact' and 'diagnosis'.

2.2.2 Impact of the Diagnostic Interval

The clinical consequences of an extended diagnostic interval on breast cancer survival are controversial. It is generally accepted that the earlier a patient is diagnosed, the better her chance of survival. Although abundant evidence has shown that a total interval (defined as symptom duration before treatment) of more than three months is associated with a worse breast cancer survival (6;23), scientific evidence does not corroborate this relationship as it relates to the diagnostic interval specifically. Most studies have found no association between the diagnostic interval and breast cancer-specific survival among symptomatic breast cancer patients (23;115-117), while others have reported a counterintuitive association: patients with delay in breast cancer diagnosis have a longer survival (118;119). This latter phenomenon is best known as the 'waiting time paradox' in the literature and has also been demonstrated for other cancer sites (120-122). Some have attributed this conflicting evidence base to the methodological differences between studies, including different intervals, study power, patient characteristics and analysis strategies (123). We think the most likely explanation is confounding by indication that can result from clinical triage, where patients with symptoms highly indicative of cancer receive more medical attention from physicians and thus have a quicker diagnosis (124). Partially accounting for this confounding effect, Torring et al. have demonstrated a u-shaped association between the diagnostic interval and survival among patients with colorectal cancer in which patients with a very short or very long diagnostic interval both had higher mortality than the rest (125). We think

a similar association may also be present in breast cancer based on the evidence of the delay being associated with stage and other prognostic factors. For example, Arndt and colleagues have displayed a u-shaped association between the duration of diagnostic work-up and the stage at diagnosis in breast cancer patients (6). Evidence from organized breast screening programs also supports this expectation as women who waited between 6 and 12 months for a diagnosis had a higher chance of larger cancers and positive lymph nodes (9;126). Recently, the International Cancer Benchmarking Partnership has been examining the association between time intervals in cancer diagnosis/treatment and survival rates (127), as delayed diagnosis was hypothesized to explain observed differences in cancer survival between countries (128;129). The result of this study may help understand the potential influence of diagnostic wait times on clinical outcomes.

The psychological consequence of the diagnostic interval on patients with suspicious cancer is substantial and incontrovertible (104;130-132). Waiting for the result of diagnostic investigations for breast cancer constitutes an intensely stressful period for women and their families. Regardless of the final diagnostic result, delay in this period often provokes anxiety, distress and fear about breast cancer (20-22). In one study, 51% of women reported being "very anxious" after abnormal screening tests (133) and such adverse psychological effects could last for several months even if a cancer was eventually ruled out (20;104;134;135). Many patients also reported experiences of "altered life priorities" and difficulty in passing time during the diagnostic interval (22). Feelings of uncertainty and the threat of cancer significantly disrupted patients' everyday life by invoking both somatic and psychological responses. Typical negative effects include insomnia, gastrointestinal upset, anxiety, fear, and inability to work, based on the qualitative evidence (21;22;136;137). In some extreme situations, the magnitude of psychological distress may reach the level equivalent to the clinical diagnosis of psychiatric morbidities (21;137-139).

Improved timeliness of diagnosis following abnormal breast screening tests has been associated with lessened anxiety among patients with benign lesions based on several intervention studies (130;134;140;141). One controlled trial showed that patients receiving immediate mammogram results reported less anxiety than those who did not (134). In another randomized controlled trial, Harcourt and colleagues found a significantly lower level of anxiety among patients in the one-stop clinic compared to those in the conventional system six days after their initial consultations (130). In contrast, some reported exacerbating distress among breast cancer patients who received prompt diagnosis at one-stop clinics, suggesting possible negative psychological effects of a rapid diagnosis for the breast cancer subgroup (130). Although the association between the diagnostic interval and the patient anxiety/distress needs to be better examined among the breast cancer subgroup, a timely diagnosis is generally considered an essential and important aspect of the patient experience.

2.2.3 Timeliness Targets

In light of the adverse consequences associated with a prolonged diagnostic interval, many jurisdictions have considered timely access to diagnosis an important indicator for system performance and have published timeliness targets for breast cancer diagnosis (142;143). As the literature contains little evidence to establish a standard benchmark for a clinically acceptable diagnostic interval, existing timeliness targets vary between jurisdictions (143). The National Health Service in the United Kingdom suggests that all patients with possible or suspected breast cancer be referred to a specialist within two weeks (144), whereas the National Initiative on Cancer Care Quality in the United States recommends that 90% of patients receive a diagnostic mammogram within 3 weeks after abnormal screening tests (143). The Public Health Agency of Canada has set national timeliness targets for abnormal screening follow-up, recommending that 90% of patients should have abnormal screening results resolved within 5 weeks (if no tissue biopsy is required) or within 7 weeks (if a tissue biopsy is required) (145;146). Many initiatives

have been introduced to facilitate a rapid diagnosis and achieve those proposed timeliness targets. One example is the development of the diagnostic assessment units (DAU) in Ontario (26;147).

2.3 Diagnostic Assessment Units in Ontario

The diagnostic assessment unit (DAU) is an organizational structure designed to provide a seamless transition from abnormality detection to definitive diagnosis (25). Ontario DAUs are comprised of the breast assessment affiliates (BAA) and independently developed regional breast assessment centres. Breast assessment affiliates (BAA) were originally developed within the organized Ontario Breast Screening Program (OBSP) to improve the integration of screening and diagnosis (26) but have expanded their services to include patients outside of the screening program. Currently, there are 47 BAAs across the province (148), and this number continues to grow as the OBSP provides incentives for facilities to become BAAs.

In the usual care scenario, the responsibility of initiating and organizing diagnostic work-up rests on the individual primary care provider. Often, patients need to travel between multiple care providers and hospitals to complete the diagnostic assessment. Common problems associated with usual care include the disconnected flow of information, limited access to resources, the lack of assurance in quality of care, and the lack of patient support, which could possibly cause poor patient satisfaction and a delayed diagnosis.

DAUs have reorganized the way that diagnostic care is delivered and have organizational components to improve the coordination of care. At BAAs, the diagnostic services are centrally provided by a multidisciplinary team, with a nurse navigator organizing and coordinating all the diagnostic assessments for each patient (27). Although primary care providers are informed of all test results, they are no longer involved in the decision-making process for further diagnostic assessment. The quality of diagnostic services provided at BAAs is ensured by the resources and expertise required by the OBSP criteria. Each BAA has sufficient capacity to provide complete imagining, surgical biopsy, and pathological assessment

of biopsy, as well as radiologists, surgeons and pathologists with expertise in breast imaging, surgery and pathology (24-27;149). The technical aspect of quality is also ensured through provision of services according to the Canadian Association of Radiologists standards. With respect to patient support, BAAs provide health education and information support to enhance patients' self-management and coping skills through a nurse navigator. Lastly, each BAA follows a formal, defined pathway and reports assessment results according to set standards (28). A detailed care map for the coordination of services with expected timeliness is also required from each BAA (149).

The other form of diagnostic assessment unit found in Ontario is the regional breast assessment centres that were independently developed. Although their configuration is less documented and regimented than the BAAs, they share the same goal of expediting the diagnostic process and are likely to have similar organizational components. Some BAAs evolved from these independent regional centres. Based on their similarities, both programs were referred to as DAUs in this study.

The hypothesized benefits of DAUs have yet to be firmly established in Ontario. The evidence base consists of three studies that evaluated DAUs' impact on consult and procedure wait times using retrospective cohort or before-and-after designs. The two before-after studies demonstrated a reduction in all diagnostic intervals studied (150;151). One retrospective cohort study reported that DAUs have a higher success rate in meeting national timeliness targets compared to usual care among women who had abnormal screening results in the OBSP (28).

Despite the evidence suggesting that DAUs can effectively reduce the diagnostic interval in organized breast screening program, little is known about DAUs' effect for patients with breast cancer at a population level. We do not know how much quicker the DAU diagnostic process is compared to usual care in breast cancer patients whose disease was detected by screening and those initially presented with signs/symptoms, nor do we know if

there are regions of the province experiencing similarly short diagnostic intervals in the absence of a DAU. We also do not know what proportion of breast cancer patients are diagnosed through DAUs and whether their coverage is population-based in the regions serviced by them. In addition, we do not know the patterns and the length of the diagnostic interval at the provincial level. We need to address these knowledge gaps to provide evidence for future program planning.

2.4 Conceptual Framework

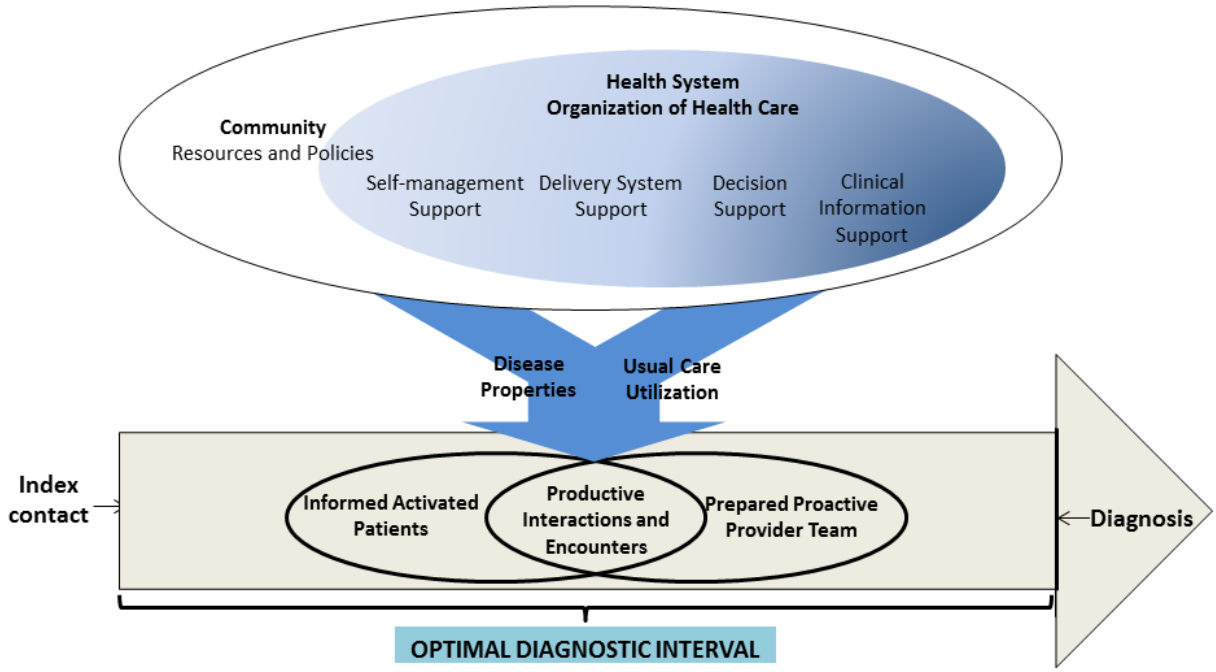
Diagnostic assessment is a complex process with multiple steps and multiple interfaces, and any factor involved in this process affects the length of the diagnostic interval. Evidence is equivocal regarding the determinants of the breast cancer diagnostic interval and, to the best of our knowledge, no previous studies have used a conceptual framework or a validated model of diagnostic care in their designs (6;16;39;42). We think a clear conceptual model is necessary to understand the role of a DAU during a diagnostic work-up and to organize study covariates based on the published evidence in the literature.

One conceptual framework that has been widely implemented to guide interventions across different healthcare settings is the Chronic Care Model (152). Although originally developed for improving chronic disease management, the Chronic Care Model has been expanded to guide interventions targeted towards disease prevention (153), population health promotion (154) and most recently the appropriate follow-up after abnormal screening tests (1). We consider the Chronic Care Model also relevant to the diagnostic assessment process as both chronic disease management and diagnostic assessment process are complex and multifaceted and both require continued interactions between physicians and patients.

The original Chronic Care Model contains four components: the health system and organization of care, community resources and policies, patients and health care providers (152). Improved chronic disease outcomes were depicted as results from effective interactions between

the informed patients and proactive practice teams, which are in turn influenced by the larger environment of the medical practice, including community and health system organization. Wagner and colleagues also listed four components in the health system for targeted interventions: delivery system design, decision support and clinical information system, and self-management, with the latter also influenced by community sources and policies.

Figure 2-2: Conceptual framework adapted from the Chronic Care Model



We have adapted the Chronic Care Model into an ecological model (Figure 2-2) to specifically fit the purpose of this study. Building on the original model, we have added a time-axis to indicate the chronological sequence of events during the diagnostic work-up. As Figure 2-2 demonstrates, the diagnostic process starts from patients' index contact with the health care system and ends at the breast cancer diagnosis. Similar to the Chronic Care Model, this framework is centred on the ideal situation whereby productive encounters occur between active patients and prepared provider teams within the context of an optimal health system, with those productive encounters ultimately leading to an optimal diagnostic interval. The diagnostic interval

is also influenced by community resources and policies that might determine interventions at the policy and organizational level (155). In addition, we have added disease properties and usual health care utilization factors into this model as both the nature of disease and the established patient-physician relationship from past health care utilization are closely related to the effectiveness of medical encounters during the phase of cancer diagnosis.

Based on this framework, factors with putative associations with the diagnostic interval in the literature were organized into following five categories: 1) patient factors 2) physician factors 3) disease factors 4) usual care utilization factors and 5) health system factors

2.4.1 Patient Factors and Breast Cancer Diagnostic Interval

Race/ethnicity, age and socio-economic status (SES) are best recognized and most frequently examined among a plethora of identified patient factors. Having African or Hispanic ethnicity in a county where the majority of the population is Caucasian is consistently related to a higher risk of a longer diagnostic interval (3;8;13;17;30-36). This association remained statistically significant after controlling for possible confounders such as age, income and insurance status. In two studies, the adjusted odds ratio associated with a longer diagnostic interval ranged from 1.39 to 1.53 for African American women compared with the white women (13;30). Evidence concerning the association between age and the length of the breast cancer diagnostic interval is relatively strong, with nine studies reporting younger age as a predictor of a longer diagnostic interval (2;3;8;12-17). Although a number of studies suggested no significant association between age and the breast cancer diagnostic interval (4;7-9;11;31;34;39;42), such negative findings were most likely explained by the different study methods, such as the restricted study population (i.e. screening population) (4;7;34;39) and the use of multivariate analyses (8;42).

The association between socio-economic status (SES) factors (education, income, employment status and insurance status) and the length of the diagnostic interval is controversial.

Overall, there is a general trend that patients of a lower socio-economic status were more likely to have delayed diagnosis (11;42;43). Bairati and colleagues found that patients with a family income of more than $40,000 per year had a 54% reduction in the odds of having a diagnostic interval beyond 5 weeks (11). Shen et al. reported low education as a predictor for a longer diagnostic interval, with the adjusted median diagnostic interval increasing by 2.3% for every 10% increase in the proportion without high school education in women's postal code area (16). Meanwhile, a number of studies did not find a statistically significant association between SES factors and the diagnostic interval (6;11;14;16;17;31;39) and some even suggested an association in the opposite direction (6). This discrepancy may be explained by the absence of a standard measurement of socio-economic status. Another possible explanation may be the difference in health care system organizations, as access to diagnostic care is less influenced by SES factors in countries with universal health coverage.

Although stronger evidence is necessary to confirm these findings, a number of other patient factors have been related to breast cancer diagnostic interval. Such factors include the number of household members (17), proximity to a hospital (16;17), language (39), psychosocial factors (1) (cultural factors, beliefs, cancer fatalism, fear coping, disease appraisal, perceived risks), urban/rural residence (8), lack of transportation (39), general health status (1), co-morbidity (16), breast self-examination habits (30), breast cancer family history (6) and benign breast disease history (16).

2.4.2 Physician Factors and Breast Cancer Diagnostic Interval

A few physician factors have been linked to the risk of a delayed breast cancer diagnosis, including age (16), the specialty of physician at first consultation (14), effective communication skills (156) and the management of the first physician (prescribe medicine vs. referral) (157). One study reported that women with localized breast cancer who had their surgery performed by older surgeons had a shorter diagnostic interval, with the median wait time decreasing by 1.5% for

every 5 years' increase in surgeon's age (16). An Italian study found a significant association between the specialty of physician at the first consultation and the length of the diagnostic interval. Among operable breast cancer patients, the odds of having a delayed diagnosis was two times greater for those who first consulted a general practitioner (GP) than those consulted a senologist who specializes in the management of breast diseases (14). Increased satisfaction with a physician's explanation of breast abnormality and cancer suspicion from the first physician were also associated with a shorter diagnostic interval. As most factors were identified in a single study, consistent findings from other studies are needed to confirm those associations.

2.4.3 Disease Factors and Breast Cancer Diagnostic Interval

Disease factors describe the characteristics of cancer, such as the clinical appearance or the underlying property/aggressiveness of cancer. Disease factors influence the productiveness of patient-physician interactions by affecting patients' and clinicians' ability to appraise the nature of the disease. The effectiveness of interactions ultimately determines the length of the diagnostic interval, as indicated in the conceptual framework (Figure 2-2).

The most frequently examined disease factors in diagnostic delay include symptoms at the first presentation, the method of cancer detection, cancer stage, tumor histology and interpretation of the first diagnostic procedure. Two systematic reviews summarizing results from 9 individual studies have concluded that having symptoms other than a lump at the first presentation was an independent risk factor for a longer diagnostic interval (2;3). According to Burgess and colleagues, patients whose presenting symptoms did not include a lump had a 3-fold increased risk of delayed referral by their GP (158). The method of cancer detection describes whether a patient was screen-detected or was detected by signs/symptoms and has been associated with a remarkable influence on the length of the diagnostic interval. Nevertheless, the direction of this association is controversial. A Canadian study found that the odds of having a delayed breast cancer diagnosis was 1.94 times greater among the screen-detected patients

compared to the symptomatic patients (11). In contrast, other studies reported a higher risk of delay among the symptomatic patients compared to the screen-detected patients, with the odds ratio ranging from 1.98 to 7.7 (13;14;29;31). These conflicts may be attributed to varying definitions of the diagnostic interval examined as well as the different clinical settings between studies. Since the diagnostic pathway is complex and is often influenced by regionally-specific policies, practice guidelines, and system configuration, simple syntheses of the international evidence on the association between the mode of cancer detection and the diagnostic interval might not be feasible or appropriate. In addition to the mode of cancer detection, an early cancer stage (33), a smaller tumor size (13;33;45) and an interpretation of first diagnostic procedure as benign were also considered important predictors for the length of the diagnostic interval, although the strength of these associations remains to be confirmed by further evidence.

2.4.4 Usual Health Care Utilization and Breast Cancer Diagnostic Interval

Patients' usual health care utilization patterns reflect their health-seeking behaviours, access to care and past relationships with health care providers. As illustrated in the conceptual framework, we consider the patient's usual use of health care as a predictor of how she will use the system in the presence of an abnormal screening mammogram or breast cancer symptoms. Among the few usual health care utilization factors examined in the literature, the source of usual care was reported to have a remarkable influence on the time to diagnosis. For example, Ferrante and colleagues (4) found that having a family physician was associated with 4.1 times greater odds of a cancer diagnosis within 60 days. Similarly, receiving usual care from a public clinic rather than a private physician was associated with a 42% increased odds of diagnostic delay, according to a study from the United States (5). Yet, as the source of usual care to a large extent is determined by the configuration of the health care system, the association between the source of usual care and breast cancer diagnostic interval remains to be investigated within the context of the Canadian health care system.

Other usual health care utilization factors have also been associated with the length of the diagnostic interval. In a population-based study from Germany (6), having a mammography history within the 12 months before the first consultation was associated with 2.3 times odds of a shorter provider delay (defined as the interval between the index contact and the start of treatment). In the ecological models proposed by Zapka (1) and Yabroff (159), patients who see their doctor more often are more likely to experience timely follow-up care after abnormal screening tests. In addition to the existing evidence from the literature, we also consider the use of preventive services and continuity of care with usual care provider relevant to diagnostic encounters as those two factors reflect patients' experience and relationship with the health care system, which can act either as a barrier or a facilitator during the diagnostic process.

2.4.5 Health System Factors and Breast Cancer Diagnostic Interval

As indicated in the conceptual framework (Figure 2-2), health system factors provide the context which enables the occurrence of productive interactions between patients and health care providers, which can ultimately lead to a shorter diagnostic interval (155). There has been a growing recognition that the achievement of timely diagnosis is dependent on resources and access to care, which involve interventions at the system and policy levels (16;152;153;155). Nevertheless, evidence of an association between organizational characteristics and their association with breast cancer diagnostic interval is scarce. The type of diagnostic facility was the most frequently identified predictor of a longer diagnostic interval at a system level. One study from Thailand (157) found that having first medical care at a provincial hospital compared with a university hospital was associated with 1.5-fold increased odds of a longer system interval (defined as the interval between the first medical consultation and the hospital admission). Studies from the United States (7;31), the United Kingdom (15) and Hong Kong (43) also found that the type of facility was significantly associated with the system interval or the time to treatment, although the categorization schemes used varied according to specific study purposes

and system designs. Other significant predictors for a longer breast cancer diagnostic interval at the system level include the size of residence population (13), hospital volume (16) and access to care (39), and they were influenced by the context of specific health care systems.

Ontario diagnostic assessment units (DAUs) contain comprehensive organizational changes to facilitate the diagnostic work-up of breast cancer. At a system level, DAUs ensure that the provision of diagnostic care is according to professional standards, the availability of diagnostic equipment and clinical expertise, and the provision of patient support as well as clinical decision-making support (24). Also, DAUs have been structured to provide diagnostic services by a multidisciplinary team that includes a nurse navigator. Therefore, we conceptualize the DAU as a health system factor and have examined its use in relation to the length of the diagnostic interval while controlling for other non-system factors.

2.5 Summary

The diagnostic period in breast cancer is characterized by multiple appointments for diagnostic tests and consultations and it often provokes considerable distress and anxiety for women and their families. A delayed diagnosis is also associated with an advanced cancer stage, more aggressive treatment and a poorer prognosis. In Ontario, effort to achieve timely diagnosis has led to the development of the diagnostic assessment units (DAUs), which are designed to improve patient experience and quality of care through seamless transitions from abnormal detection to the definitive diagnosis. However, the actual duration of the diagnostic interval at the population level and the relative effectiveness of DAU versus usual care in achieving a timely diagnosis for breast cancer patients remain unclear. Therefore, understanding the association between DAU use and the timeliness of breast cancer diagnosis is necessary to provide evidence for program planning and will eventually lead to improved patient experience and clinical outcomes.

Chapter 3

Methods

3.1 Study Purpose and Objectives

The purpose of this study was to describe and compare the length of the diagnostic interval for breast cancer patients diagnosed through a diagnostic assessment unit (DAU) versus those diagnosed through usual care (UC) in Ontario. This study also aimed to provide information on DAU use as well as the length of the diagnostic interval for breast cancer patients in Ontario. Specifically, this study had three objectives:

1. To describe the length of the diagnostic interval and DAU coverage at a provincial level, and also describe their geographic variation by county;
2. To examine the association between DAU use and the diagnostic interval in breast cancer patients whose disease was detected by screening;
3. To examine the association between DAU use and the diagnostic interval in symptomatic breast cancer patients.

3.2 Hypotheses

One of the stated objectives of DAUs is to shorten diagnostic wait times through the coordination of care, better resource availability and access to multidisciplinary expertise (160). Previous studies have reported quicker diagnoses for patients involved with interdisciplinary care models (161), patient navigators (150;162;163) or direct-referral programs (164;165). We proposed the following research hypotheses based on a review of the literature: 1) there was regional variation in the length of the diagnostic interval and DAU use, and counties with a higher DAU coverage rates were expected to have shorter diagnostic intervals 2) women diagnosed through DAUs had a shorter diagnostic interval than those diagnosed through usual care (UC) among breast cancer patients whose disease was detected by screening 3) women

diagnosed through DAUs had a shorter diagnostic interval than those diagnosed through UC among breast cancer patients who initially presented with signs/symptoms.

3.3 Design Overview

This was a population-based retrospective cohort study of all female patients diagnosed with invasive breast cancer in Ontario, Canada in a one-year period. Study data were obtained from administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) Queen's Health Services Research Facility, which is a satellite unit of ICES with additional data (the Collaborative Stage Data and the most recent Ontario Cancer Registry and Ontario Breast Screening Program data) requested from Cancer Care Ontario (CCO) and linked to ICES data. A list of BAA hospitals was provided to us by the OBSP and a separate list of regional breast assessment centres was obtained through an email survey to Cancer Care Ontario Regional Primary Care Leads and the OBSP Regional Program Managers. Using the list of DAU hospitals and administrative databases, we were able to develop an algorithm to determine a diagnostic route (DAU versus UC) for each patient and measure their diagnostic intervals. Though factors affecting DAU use are unclear, we expected that DAU use was largely determined by the geographic residence of the patient and/or their referring physician's practice location. As such, this study constitutes a natural experiment whereby characteristics of women diagnosed through a DAU versus those who were not were expected to be similar. However, potential confounders of the association between DAU use and breast cancer diagnostic interval were considered, as we could not rule out the imbalanced distribution of covariates between the DAU and UC groups. In particular, we studied screen-detected patients separately from those who initially presented with signs/symptoms as the diagnostic process and the ultimate advice we provide from our findings may differ across those two settings.

3.4 Student's Contribution

The student was responsible for the study design, CCO data request, data management and the statistical analysis. Data management involved the preparation and execution of a detailed dataset creation plan (attached in Appendix A) across multiple databases. Ms. Marlo Whitehead, a senior analyst at ICES Queen's, performed the database linkages and created the study dataset using the dataset creation plan. Many of the independent variables needed for this study were being derived for Dr. Patti Groome's larger study on breast cancer peri-diagnostic episode of care, so the student benefited from some synergies with that work. Using the study dataset created by Ms. Whitehead, the student created a working dataset which included the derivation of variables specific to this study.

3.5 Study Population

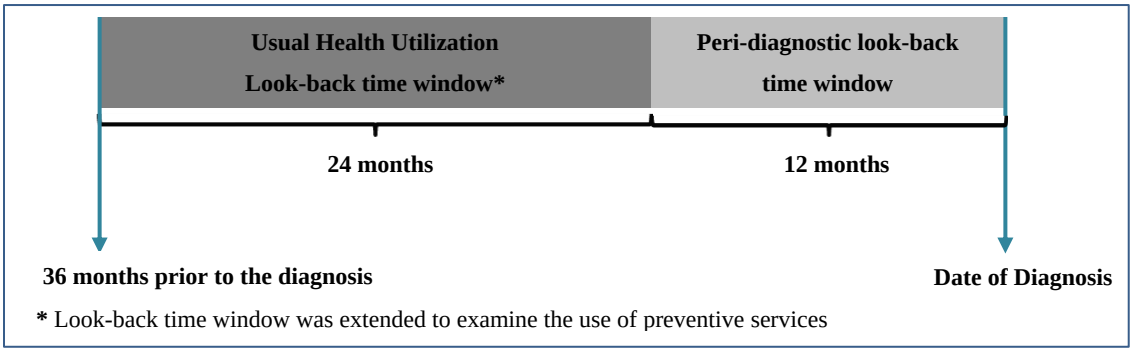
We used the Ontario Cancer Registry (OCR) to identify all female patients in Ontario who were diagnosed with invasive breast cancer (International Classification of Diseases Diagnosis Codes - Version 9 (ICD-9) codes: 174.0 to 174.9) between Jan 1st, 2011 and December 31st, 2011. We chose this study period because of the newly introduced Ontario Health Insurance Plan (OHIP) fee codes (effective since Oct 1st, 2010) that distinguish the purpose of a mammogram as being screening versus diagnostic. Inclusion criteria were: 1) female patients 2) histologically confirmed invasive breast cancer and 3) a single primary cancer. Among eligible patients identified from the OCR, we excluded patients 1) whose cancer was diagnosed by death certificate only 2) who were living outside of Ontario at the time of diagnosis and 3) who did not have OHIP coverage for at least three years prior to the diagnosis for the purpose of measuring patients' usual health care utilization.

3.6 Study Timeframe

We defined the starting point of the look-back as the diagnosis of a single, primary invasive breast cancer between Jan 1st, 2011 and Dec 31st, 2011. The look-back time window was

divided into two sub-intervals. The first sub-interval consisted of a 12-month look back from the date of breast cancer diagnosis to identify the index contact. While the abnormal Ontario Breast Screening Program (OBSP) screening tests were identified within 12 months before diagnosis, the rest of breast-related procedures were identified using a 6-month look-back time window based on our observation that less than 5% of OBSP screen-detected patients had a diagnostic interval greater than 6 months (see Appendix B). The second sub-interval was used to collect information about patients' usual health care utilization. Previous evidence suggests that a two-year look back period provides stable estimates of usual health care utilization (166). As evidence shows that patients have a significantly increased utilization of health care services prior to diagnosis (166;167), we decided to look 24 months further back from the first 12-month peri-diagnostic interval to capture usual health care utilization characteristics, with extensions of the time window to examine the use of cancer screening services (see Figure 3-1). Therefore, the study timeframe consisted of a total of 36 months prior to the date of the breast cancer diagnosis for each individual patient.

Figure 3-1: Study timeframe

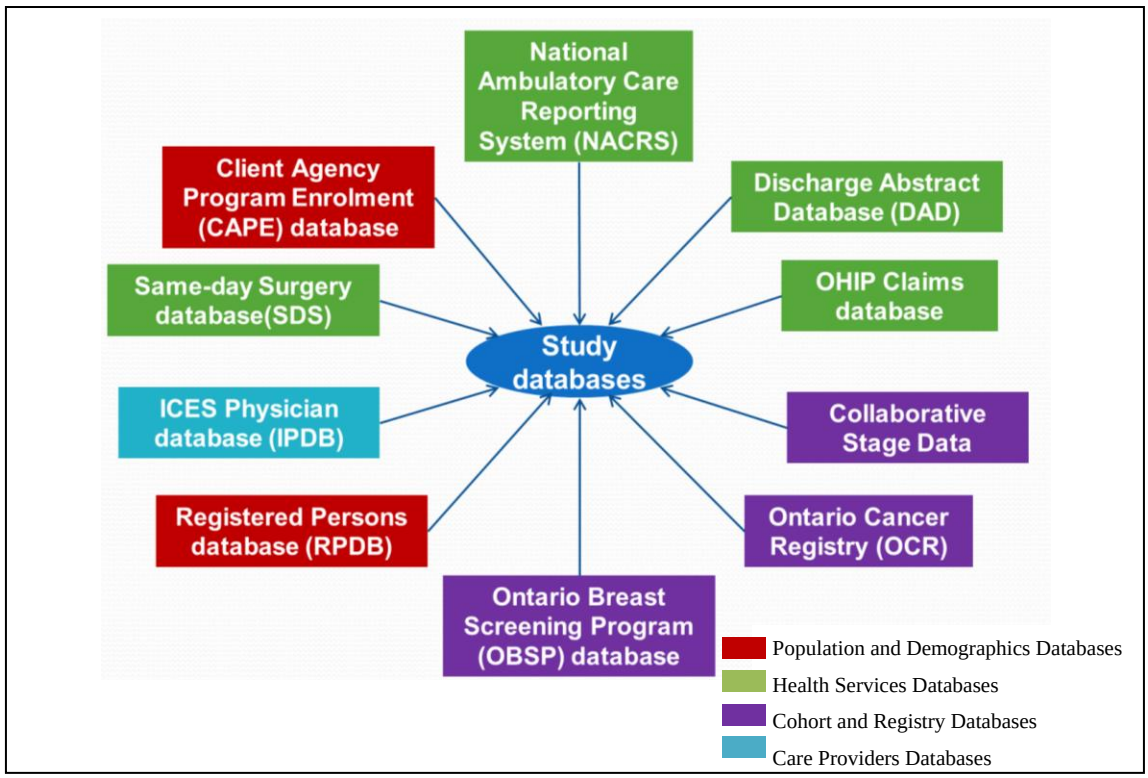


3.7 Data Sources

Data in this study were obtained from the following administrative databases: 1) Client Agency Program Enrolment (CAPE) 2) Canadian Institute for Health Information Discharge Abstract Database (CIHI/DAD) 3) ICES Physician Database (IPDB) 4) National Ambulatory

Care Reporting System (NACRS) 5) Ontario Breast Screening Program (OBSP) database 6) Ontario Cancer Registry (OCR) database 7) Ontario Health Insurance Plan Claims Database (OHIP) 8) Collaborative Stage Data 9) Registered Persons Database (RPDB) and 10) Same-day Surgery Database (SDS). All of above databases are housed at ICES, with the exception of the stage data, the most recent OCR data, and the most recent OBSP data that were directly requested from CCO and linked to ICES data for analyses. All databases except for geo-coded information are linkable at an individual level with an anonymous ICES Key Number (IKN) (See Figure 3-2).

Figure 3-2: Study data sources



A detailed description of data sources and their use to identify study variables is presented below:

3.7.1 Client Agency Program Enrolment (CAPE)

Currently, there are a number of different primary care models in Ontario and the CAPE contains information on the specific type of primary care model an individual was enrolled in, the start and end date of program enrolment, and the associated physicians (168). In this study, the

CAPE was used to determine whether the practice setting of the referring physician was a rostered practice or a non-rostered practice and it was also used to determine the primary care provider for each patient.

3.7.2 The Canadian Institute for Health Information/ Discharge Abstract Database (CIHI/DAD)

The CIHI/DAD captures all hospitalizations at acute care, rehabilitation care, chronic care and day surgery institutions in Ontario (169). The accuracy of the CIHI/DAD data in Ontario has been previously assessed by examining the concordance between the CIHI/DAD and re-abstracted medical records (170). The agreement was shown to be excellent (greater than 97%) for non-medical variables (gender, birth date, health care number, and admission date) and good (85%) for diagnostic codes. Exact agreement rate was 91.3% for Canadian Classification for Health Intervention (CCI) codes and 89.9% for significant diagnoses coded using International Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) (171). The CIHI/DAD database was used to determine the type of diagnostic procedures (mammogram, MRI, breast ultrasound, and breast biopsy), associated physicians and diagnoses coded using the ICD-10-CA. The CIHI/DAD was also used to obtain information on the diagnostic institutions, date of hospital admissions and number of hospital admissions.

3.7.3 ICES Physician Database (IPDB)

ICES Physician Database contains yearly information of all physicians in Ontario, including physician demographics, education, specialty and practice locations (172). The IPDB database was used to determine the referring physician's demographics (age, gender), their years in practice, specialty, and their yearly clinical volumes. The IPDB database has been validated against the Ontario Physician Human Resource Data Centre database, which frequently verifies information through direct contact with physicians in Ontario (172).

3.7.4 National Ambulatory Care Reporting System (NACRS)

The NACRS is a national database that captures patient visits to hospital and community based ambulatory care, including outpatient clinics and emergency departments (173). The data quality of the NACRS submitted by Ontario facilities was evaluated in a re-abstraction study (174). There was an overall good agreement for demographic and administrative data, and the agreement rates on coding the main problem and the reason for visit were 68.8% and 59.3%, respectively. The agreement rates were higher for the selection of main problem (85.5%) and the selection of the reason for visit (72.5%). With respect to interventions, there was a 90.4% agreement for all CCI codes and an 80.9% agreement rate for the selection of the main intervention. The NACRS was used in combination with the OHIP, CIHI/DAD data to identify all the diagnostic procedures, their dates and diagnostic institutions, disease history, and health care encounters. The NACRS was also used to identify those patients who were presented to health care system through an emergency department.

3.7.5 Ontario Breast Screening Program Data (OBSP)

The OBSP data contains information of all women who are enrolled in the OBSP program (175). We used the Client, Screening and Cancer entities from the OBSP data combined with the OHIP data to assign the method of cancer detection (screen-detected versus symptomatic) and to determine the use of breast cancer screening services. We also used the OBSP data to validate our strategy of determining DAU use, as the OBSP keeps track of the OBSP clients who were assessed through a DAU (BAA) for payment purposes.

3.7.6 Ontario Cancer Registry (OCR) database

The Ontario Cancer Registry captures all registered incident and mortality cancer cases (except non-melanoma skin cancer) in Ontario (176). The estimated completeness of the OCR for all sites combined exceeds 95% based on one study using the capture-recapture methodology (177). The date of diagnosis in the OCR is defined as the date of earliest diagnosis of the primary

site of cancer for that patient (176). Hall and colleagues found a 91.5 % match for date of diagnosis within one month in the OCR compared to a prospective clinical database using a cohort of head and neck cancer patients (178). In this study, the OCR was used to identify the study cohort and determine the date of cancer diagnosis, cancer histology, the source of cancer diagnosis, and patients' residence at the time of diagnosis (166;176).

3.7.7 Ontario Health Insurance Plan Claims Database (OHIP)

The OHIP database contains all billing claims made by physicians (and other health care providers) for insured services provided to the residents of the province. Approximately 94% of Ontario physicians are paid on a fee-for-service or blended basis and submit claims to OHIP for reimbursement (179). The OHIP claims contain information on the type of service provided, diagnostic information, physician who provided the service, individual that received the service, date that it occurred, and the associated fee code. The quality of the OHIP data has been examined in one study among a cohort of node-negative breast cancer patients (180). The overall agreement for the procedure codes was 95.4%, when the OHIP claims for the most definitive procedure were compared with the abstracted medical charts. The agreement rate was 98.1% when only breast surgery codes were compared. In this study, the OHIP data were used to assign the method of cancer detection and were also used in combination with the NACRS, CIHI/DAD and Same-day Surgery (SDS) data to identify diagnostic procedures, associated physicians, dates when the services were delivered, usual health care utilization, and past disease histories.

3.7.8 Collaborative Stage Data

The Ontario Collaborative Stage Data captures a comprehensive range of data items from clinical medical records and pathological reports for four most common cancers (breast, colorectal, prostate, and lung) across Ontario using a Collaborative Stage Data Collection System (181-184), which allows the assignment of the AJCC TNM stage classification (181;182). Of all incident breast cancer cases diagnosed in 2010, 93% had valid stage

information captured in this database (185). In this study, the Collaborative Stage Data was used to determine detailed information on breast cancer staging (including tumor size) and the histological grade of cancer (tumor aggressiveness). The quality of the Collaborative Stage Data specific to breast cancer has previously been assessed by Cancer Care Ontario, which reported the reliability as "very good" with a Krippendorff's Alpha ranging from 0.81 to 0.85 across three scenarios studied (185).

3.7.9 Registered Persons Database (RPDB)

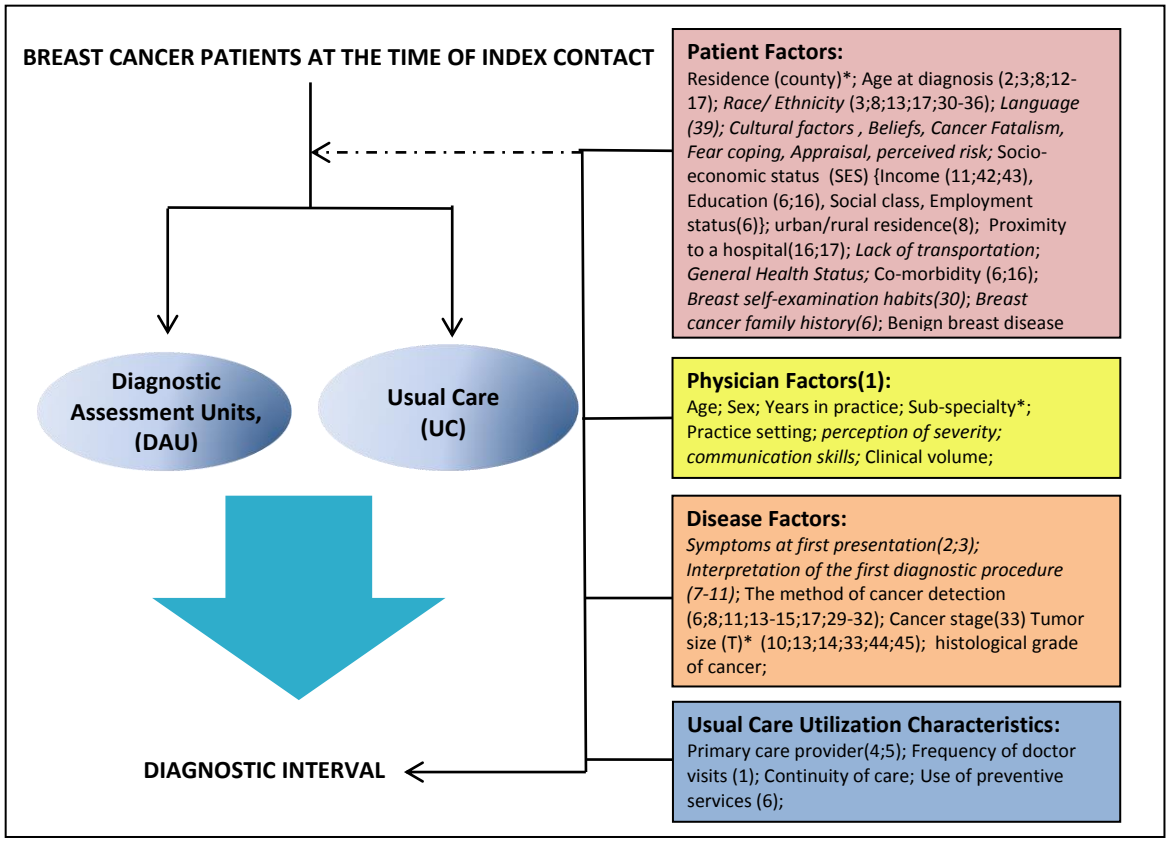
The Registered Persons Database (RPDB) is a population-based registry that contains patient demographic information and captures changes in the eligibility period for individuals who ever received an Ontario health insurance card (186). Personal identifying information is removed when the RPDB data arrives at ICES and each unique health number is converted into an anonymous identifier (IKN). The RPDB was used to determine eligibility for this study and provide information on patient demographics. Although the RPDB provides good information on sex and birth date (187), the postal code data are often outdated as individuals are not required to inform Ontario Ministry of Health and Long-Term Care (MOHLTC) of their changes in address (186). Therefore, the RPDB was used in combination with the OCR to assign postal codes for patients, with the preference given to the latter.

3.7.10 Same-day Surgery Database (SDS)

The SDS database has been separated out from the NACRS database at ICES since 2003 (188). This dataset provides information on patients' demographics (date of birth, sex, postal code, county and residence codes), clinical data (diagnoses, procedures, physicians) and administrative data (institution/hospital number, length of stay, admission dates, etc.) (188). The SDS was used in combination with the CIHI/DAD and NACRS data to identify breast-related diagnostic procedures, associated dates and institutions, disease histories, and health care encounters.

3.8 Study Variables

Figure 3-3: A detailed display of study variables



Italics-information not available in administrative databases;

*variables for description purposes and not controlled for in the multivariate analysis.

Figure 3-3 was derived from this study's conceptual framework (Figure 2-2) and contains a detailed description of all covariates and their relationship with DAU use and the length of the diagnostic interval. These relationships were postulated based on our understanding of the system and/or on the existing evidence, with references to the literature provided in the figure. We only had information on a subset of these variables as indicated in the figure, since we were restricted to using administrative databases. We expected balanced distributions of most covariates between two diagnostic routes (DAU vs. UC) as the study constitutes a natural experiment where DAU use is mostly likely determined geographically. Nonetheless, available covariates were investigated and controlled for as potential confounders. As Figure 3-3 illustrates, covariates in

this study were classified as 1) patient factors 2) physician factors 3) disease factors 4) usual care utilization factors. Definitions and measurements of variables are described below with a summary table provided in section 3.13.

3.9 Diagnostic Interval

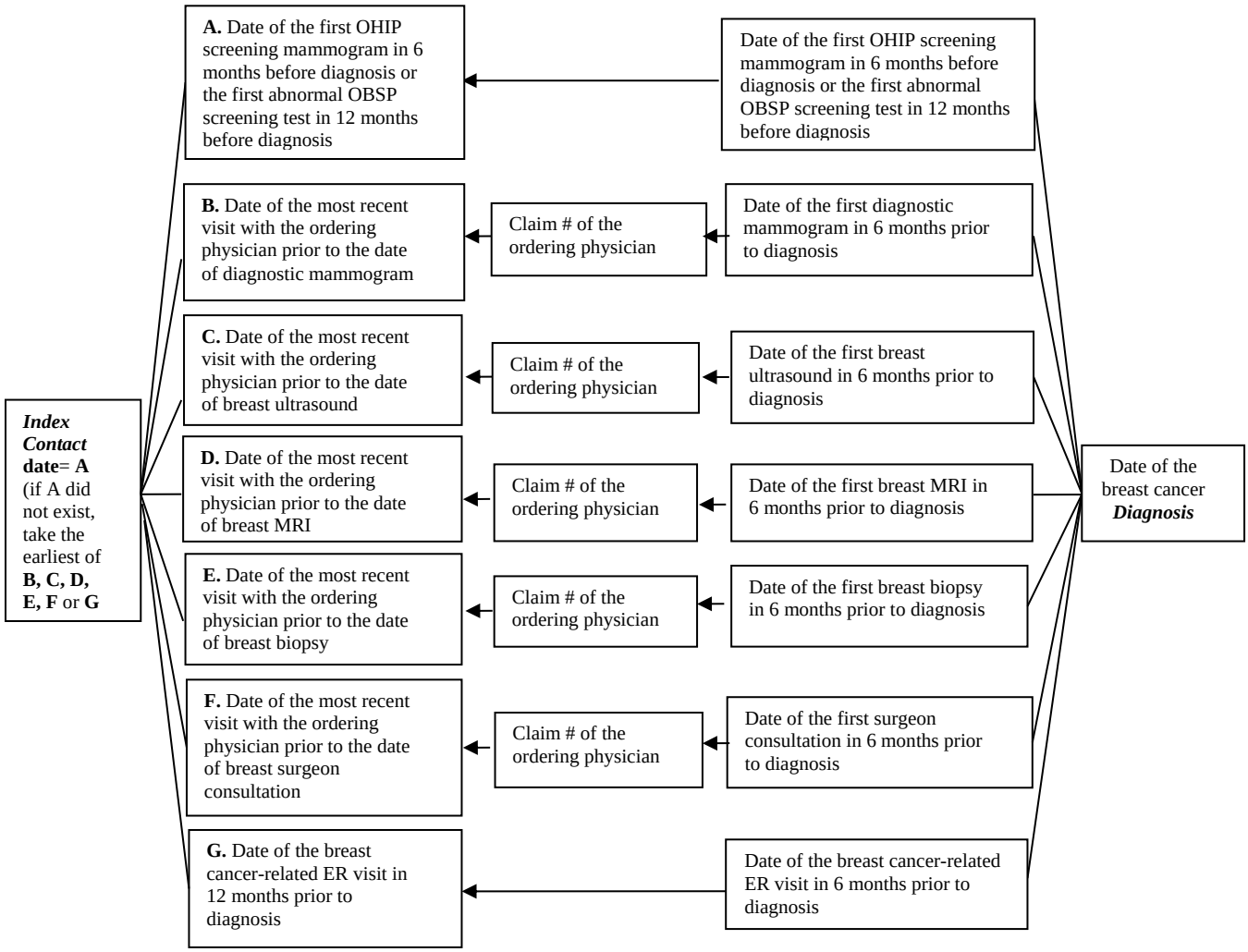
The measurement of the diagnostic interval depended on identifying the index contact when the earliest breast abnormality was noticed by the health care system. The identification of the index contact was difficult in that administrative databases do not provide results. One solution was to identify the earliest diagnostic procedure and the referral visit within a defined period of time (114). We decided to adopt a 6-month look-back time window based on the evidence from the Canadian Partnership Against Cancer (145;146), results of previous studies (189), clinical expert opinion, as well as our observation using the OBSP data (see Appendix B) that less than 5% of abnormal mammograms occurred in the 6-12 months prior to diagnosis . Since test results were available in the OBSP, we used a 12-month look-back time window for identifying abnormal OBSP screening tests.

Our detailed strategy is illustrated in Figure 3-4. We first identified the date of diagnosis using the Ontario Cancer Registry database (OCR). Then we worked backwards in time to identify various breast-related procedures and physician visits using information obtained from the OHIP, CIHI/DAD, SDS and NACRS databases. We identified the earliest record for each breast-related procedure or visit, which included screening mammogram, diagnostic mammogram, breast ultrasound, breast magnetic resonance imaging (MRI), breast biopsy or breast surgical consultation, and breast-related emergency department visits. We worked further back for all breast-related diagnostic procedures and identified the most recent visit to the referring physician who ordered that procedure. We assigned the index contact date as the earliest screening date (A) if a patient ever had a screening mammogram within the defined time period, regardless of the other tests. The index contact was assigned using the earliest date among dates (B-G) for patients

without a one-year screening history. The diagnostic interval was subsequently calculated as the number of days between the index contact, and it was kept continuous for analyses.

The Public Health Agency of Canada has set national timeliness targets for abnormal screening follow-up, recommending that 90% of patients should have abnormal screening results resolved within 5 weeks (if no tissue biopsy is required) or within 7 weeks (if a tissue biopsy is required) (145;146). Since our study was restricted to a subset of breast cancer patients and a tissue biopsy was needed to establish a cancer diagnosis, the diagnostic interval was also dichotomized at 7 weeks for analyses.

Figure 3-4: Measurement of the diagnostic interval



3.10 DAU Use Determination

To accurately determine if a patient was diagnosed through a DAU or through usual care (UC) was challenging in that there is no systematically collected information on the patient involvement with breast DAUs outside of the OBSP. The determination became even more difficult as we did not know at which point patients were referred to a DAU and DAU use may occur at any time during the diagnostic work-up.

Rather than trying to use the entry point to determine DAU use, we decided to make the determination based on the diagnosing hospital. We made this choice because the institution where the index contact occurred (usually a mammogram) is not normally recorded in our data sources because those services are not normally delivered in a hospital setting. In using the diagnosing hospital, we assumed that patients were unlikely to quit a DAU once entering the system so that hospital represents the location of the entire diagnostic process. The diagnosing hospital for each patient was determined based on the institution where the biopsy or therapeutic surgery closest to the date of diagnosis was performed, using information obtained from the OHIP, NACRS, SDS and CIHI/DAD databases. The other reason we decided on this strategy was because information on the biopsy/surgery hospital was more likely to be complete, as biopsy/surgery was necessary to establish the cancer diagnosis for all patients in this study.

We identified which patients were diagnosed through a DAU using two different lists comprised of 1) the OBSP breast assessment affiliate (BAA) hospitals and 2) independently developed regional breast assessment centres (see Appendix C). The OBSP provided us with their list of BAAs with operational start and end dates (190) We developed a list of independent regional breast assessment centres by surveying the Ontario CCO Regional Primary Care Leads and the OBSP Regional Program Managers. In some instances, OBSP BAAs were officially established during the year 2011. We considered patients diagnosed through a BAA only if the official start date was before the patient's index contact date.

We validated our algorithm in determining use of DAU using a separate information source on the OBSP screen-detected patients (see Appendix C), as the OBSP tracks patients diagnosed through official BAAs for payment purposes. The final DAU use was determined using a hierarchy: 1) for OBSP screen-detected patients, the BAA use was ascertained using the payment records from the OBSP dataset. Among those OBSP screen-detected patients without a BAA payment record, their diagnosing hospitals were compared with the list of regional breast assessment centres to determine the use of regional breast assessment centres; 2) for the rest of the patients, DAU use was determined using our validated algorithm based on diagnosing hospitals. In addition, we further distinguished between BAAs and non-OBSP DAUs with the latter given separate considerations in a sensitivity analysis.

3.11 Stratification Variable: Method of Cancer Detection

Each patient was assigned a method of cancer detection depending on the type of the index contact as indicated in the Figure 3-4. If the index contact was Date A (screening mammogram), the breast cancer patient was screen-detected. Otherwise, we considered the patient presented with signs/symptoms (symptomatic).

We investigated the association between DAU use and the diagnostic interval separately for screen-detected patients (Objective 2) and symptomatic patients (Objective 3) in this thesis. We made this decision based on two reasons. First, previous evidence suggests that the method of cancer detection is an effect modifier of the association between many other factors and the length of the diagnostic interval (11;29;31). It is possible that the association between DAU use and the length of the diagnostic interval also differs by the method of cancer detection, as we expected the diagnostic pathway to be different for screen-detected patients and symptomatic patients. Second, the health system organizes these two groups differently. For instance, the majority of screen-detected patients were from the OBSP and their diagnostic intervals were monitored as the program has timeliness targets for abnormal screening follow-

up. On the contrary, the symptomatic patients were unattached and their diagnostic experiences were less well tracked or assessed by the current system. Thus we consider studying them separately as situation-specific recommendations would be more appropriate for knowledge translation purposes. In addition, we were concerned that a small group of symptomatic patients who presented to the health system through the emergency department (ED) may have different chance to use a DAU. As the number of ED-detected patients was small, we decided to exclude them from our analyses.

3.12 Covariates

3.12.1 Patient Factors

Patients' active co-operation and compliance with clinical decisions are crucial to the timeliness of a cancer diagnosis. We investigated and controlled for patients' characteristics as potential confounders, with the exception of the residence variable that was used for descriptive purposes only (Objective 1).

Residence and Age: Patient's residence and age were obtained using information from the RPDB and the OCR databases. Each patient was assigned one of 49 counties of Ontario using the ICES macro (191) based on patient's postal code at diagnosis. Patient's residence was only used for describing the geographic variation of the diagnostic interval and DAU use and was not included in the analyses. Patient's age at diagnosis was calculated as years between the date of birth and date of cancer diagnosis.

Recent Immigration Status: Patients who achieved the landed immigrant status within ten years of diagnosis date were considered recent immigrants (192). We used the same approach as Lofters and colleagues to ascertain the immigration status using dates of OHIP registration as a proxy for dates of immigration to Canada (193). Over 70% of people who registered with OHIP within ten years prior to the diagnosis date were assumed to be immigrants and the rest were assumed to be interprovincial migrants or immigrants originally

landed in another province (193). We considered the accuracy of this proxy measure acceptable for assessing a covariate and thus assigned the recent immigration status as Yes/No using Lofters' approach and the RPDB database.

Socio-economic Status: Socio-economic status was measured using a validated material deprivation index (194-196). This index measures area-level socio-economic status based on the census Dissemination Area (DA), which is a small area composed of one or more neighboring blocks with a population of 400 to 700 persons (197). We first assigned patients to DAs using the ICES macro based on postal codes and then assigned a standardized deprivation index score (with a mean of 0 and a standard deviation of 1) for each patient using the ICES electronic lookup table of DA-level index scores (2006) (195). Areas with higher scores are more deprived than those with lower scores.

Urban/Rural Residence: Urban/rural residence was measured using the Rurality Index for Ontario 2008 (RIO 2008), which is an ordinal and broad measure of rurality (198) and has been validated and implemented in a number of programs by MOHLTC and Ontario Medical Association (OMA) (199). We assigned an integer RIO 2008 score (ranging from 0-100) to each patient by running the ICES macro based on the Census Subdivision (CSD), which was assigned for each patient using the postal code. A higher RIO 2008 score reflects a higher degree of rurality. Patients with RIO 2008 scores greater or equal to 40 or with missing RIO 2008 scores but valid CSDs were classified as rural. Non-missing RIO 2008 scores less than 40 were categorized as urban, in accordance with MOHLTC's definitions (200).

Co-morbidity: Co-morbidity was evaluated using the Johns Hopkins Aggregated Diagnosis Groups (ADGs) (201). The validity of ADGs using administrative databases has been demonstrated in previous studies in Ontario (201;202). Each ADG represents one cluster of diseases with similar clinical criteria and expected needs for health care (203). Individual diseases or conditions with valid ICD (Version 9 or 10) diagnosis codes in the administrative

databases can be placed into a single ADG, and each individual patient may be assigned up to 32 ADGs over a defined period of time. An ICES macro was used to obtain ADGs from patients' diagnosis codes using the OHIP and CIHI-DAD databases (204). We then calculated the total number of ADGs for each patient between 36 months and 12 months before diagnosis, in accordance with previous studies (205-208). We initially examined the frequency distribution of the total number of ADGs and then categorized the ADGs by quintiles into 0-3, 4-5, 6-7, 8-9 and more than 10 ADGs.

Benign Breast Disease History: A history of benign breast disease has been associated with a longer diagnostic interval from the first diagnostic procedure to surgery (16). We adopted a three-year time window before the date of diagnosis was adopted based on previous work (16). We examined all the ICD-9/ICD-10 diagnostic codes recorded in the OHIP (179), CIHI/DAD, SDS and NACRS databases between 48 months and 12 months prior to diagnosis to identify the benign breast disease history. A dichotomous value Yes/No was used to assign benign disease history for each patient for analyses.

3.12.2 Physician Factors

Physician's characteristics have been associated with abnormal screening follow-up in Zapka's review (1), and might also be associated with the length of the diagnostic interval. In the context of this study, only the referring physicians were characterized because of their possible influence on DAU use. Other physicians were considered components of DAU or UC and thus their characteristics would not be controlled. We defined a referring physician as the health care provider who initiated the diagnostic assessment and this referring physician was identified using the OHIP and NACRS databases. Referring physicians' characteristics were only examined and controlled for among breast cancer patients with sign/symptoms. This is because the OBSP did not require a referring physician except for the initial screening and some OBSP screening centres directly arrange diagnostic assessment without re-referral from family

doctors (90). It's not feasible or appropriate to control for the referring physician for the screen-detected subset.

Physician Demographic Variables (Age and Sex) Age and sex of the referring physician were ascertained from the ICES Physician Database (IPDB). Age was calculated as years between physician's date of birth and the date of patient's cancer diagnosis. Physician's sex was dichotomized as male and female.

Physician Clinical Practice Variables included physician's years in practice, subspecialty, clinical volume and the practice setting. All the information was obtained from the IPDB database except for the practice setting, which was available in the CAPE database.

Physicians' years in practice was calculated as number of years from physicians' graduation to the patient diagnosis. This data element in the IPDB is directly obtained from the Ontario Physician Human Resources Centre (OPHRDC). Its current validity has yet to be assessed (172). Physician's subspecialty was defined as the functional specialty of physicians over the longest period of their practice. This subspecialty assignment has been validated by telephone interviews among a random sample of physicians (172). Sub-specialty of referring physician was classified as GP/FP, diagnostic radiologist, surgeon and others for descriptive purposes and not included in the multivariate analysis. Physician's clinical volume reflects the workload of a referring physician, and it was measured as the total number of visits per physician in the fiscal year studied.

The practice setting indicates if a patient was rostered to a referring physician who belongs to a primary care program (209), where services are often delivered by a team of primary care providers. Having the referring physician involved in such a group practice might affect patients' chance of using a DAU due to the influence by the practice team. Therefore, the practice setting was classified as rostered practice or non-rostered practice using the CAPE

database for referring physicians whose main specialty fell under primary care. Referring physicians who had other specialties were classified as a separate group for analyses.

3.12.3 Disease Factors

Cancer manifestation determines the time to diagnosis by influencing patients' and clinician's ability to appraise the nature of the disease. We did not have information on the appearance of the disease (detailed signs/symptoms) or doctors' interpretation of diagnostic tests. We only had information on the cancer histology and cancer stage information for each individual patient. As many of the descriptors of the cancer were only available at the time of diagnosis and some factors may change over time, we controlled for the relatively static aspects of disease (histological grade and cancer stage group) and described the distribution of one non-static factor (tumor size) in detail contrasting patients in the DAU and UC groups.

***Histological Grade of Cancer*:** Tumor grade describes the aggressiveness of a tumor based on its differentiation and proliferative activities (41). We assigned a histological grade for each patient using the Nottingham Grading System (210-213). Bloom-Richardson (BR) score is a scale ranging from 3 to 9 with a higher score indicating a poorer differentiation (214) and it can be converted to the Bloom-Richardson grade (215). Histological grade of breast cancer was assigned as low, medium and high using the information obtained from the Collaborative Stage data at Cancer Care Ontario.

Cancer Stage: Cancer stage describes the extent the disease has spread within the body and is widely recognized as the most important prognostic factor (216). Cancer stage in this study was defined using the AJCC Tumor-Node-Metastasis (TNM) staging system, 7th edition (181;182). We classified cancer stage as Stage 0-I, Stage II and Stage III-IV for analyses, based on considerations about clinical detectability and on its frequency distribution. In order to better understand the distribution of disease factors, we also categorized tumor size and described it

separately for the DAU group and the UC group using information obtained from the Collaborative Stage Data.

3.12.4 Usual Care Utilization Characteristics

Characteristics of usual care utilization reflect patients' health seeking behaviours, patients' access to care and interrelations with health care provider, which are key components in predicting the effectiveness of future health care encounters and subsequently the length of the diagnostic interval. We looked back between 36 months and 12 months from the date of diagnosis as the '*usual care utilization period'*, since a two-year look back period was suggested as providing a stable estimate of usual health care utilization (166). However, the look-back period was extended to measure the use of preventive services especially for cancer screening services, as some recommended screening intervals are longer than two years. Characteristics of usual care utilization were examined as potential confounders of the association between DAU use and the diagnostic interval.

***Frequency of Doctor Visits*:** The frequency of doctor visits describes patients' usual health care utilization and access to care and was measured by counting the total number of health care encounters that occurred during the two-year period, including office-based visits, emergency department visits and hospital admissions. We used the same algorithms developed in Leung's thesis to capture medical encounters from different sources of databases (166). Office-based visits were defined as consultations and physician visits occurred at office, home, phone, long-term care or undefined places, and they were captured in the OHIP databases with the practice location ascertained using an ICES macro (217). The number of emergency department visits and the number of hospital admission were counted using information in the NACRS and CIHI-DAD databases, respectively. For office-based visits and emergency department visits, we aggregated claims that made by the same physician on the same date as one visit.

***Primary Care Provider*:** Having a general practitioner (GP)/ family physician (FP) has been associated with a shorter diagnostic interval in the United States (4), but there is no comparative evidence in Canada and we do not know if having a primary care provider is associated with DAU use. Based on the Primary Care Access Survey, approximately 92% of the Ontarians reported an affiliation with a primary care provider in 2011(218). Currently, there is no standard approach to determine if a patient had a primary care provider using Ontario administrative data. We adapted algorithms from previous studies (219;220) based on the reality of Ontario's administrative databases and determined the GP/FP attachment status of each patient using information from the CAPE and OHIP billing databases. The patient was considered having a FP/GP if she had any of these three situations during the two year look-back period: 1) continuously enrolled to a primary care provider; 2) at least two visits to the same GP/FP; 3) at least one visit to a GP/FP for an annual health examination. Otherwise, the patient was not attached to any primary care provider. The primary care provider was dichotomized as Yes/No for analyses.

Continuity of Care: Continuity of care describes the care an individual patient received over time and it has been considered an important aspect of the primary care (221;222). We measured the continuity of care using the Usual Provider of Care (UPC) index (223), which is defined as the proportion of visits to the most often visited provider over the two-year '*usual healthcare utilization period'*. The UPC index was derived using the algorithm developed and validated by ICES (207). We only calculated the UPC index for patients with at least three visits during the two-year period because the UPC index falsely overestimates the continuity of care for low-users (222;224). Patients who had less than three visits or without a usual care provider were classified as a non-user group (225) and patients with a UPC index score greater than 0.75 were classified as having high continuity of care (207).

Use of Preventive Services: Use of preventive services was measured using the preventive services index that was generated to estimate the overall propensity for using preventive health care (166). The preventive services index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible (166). Five component preventive services involved in calculating this index were annual health examination, influenza vaccination, breast cancer screening, colorectal cancer screening, and cervical cancer screening. Annual health examination and influenza vaccination status were assessed for the entire study population during the two-year look back period. Annual health examination was identified using OHIP fee codes along with diagnostic codes for adult annual health examination in OHIP databases, defined by the General Preamble of OHIP fee schedule (226). The influenza vaccination status was ascertained using the method described by Kwong (227) and Leung (166) using OHIP fee codes. The study period was extended for assessing cancer screening services, using the length of recommended screening interval plus one-year buffer period to ensure the capture of service utilization. Only patients who were eligible for at least one year to receive cancer screening services were assessed, with the age eligibility criteria defined by each cancer screening program in Ontario. The use of each type of preventive service was assigned a dichotomous value (Yes/No), with their distribution described and compared between patients in the DAU and UC groups.

3.13 Summary of Study Variables

Table 3-1 summarized all variables in this study with information on variable names, types, data sources, and the format for analyses.

Table 3-1: Study variables

Variable	*Type*	*Source*	*Format for Analyses*
Outcome			
Diagnostic Interval	Continuous	OHIP, CIHI-DAD, SDS, NACRS	
Exposure			
DAU Use	Dichotomous	OHIP, CIHI-DAD, SDS, NACRS, OBSP(SCREENING)	Yes/No
Patient Factors			
Age	Categorical	RPDB	<50 50-59 60-69 70-79 80+
Immigration Status	Dichotomous	RPDB	Yes/No
Deprivation Index	Categorical	RPDB, OCR	Deprivation Index Quintile 1 (lowest) 2 3 4 5 (highest) Missing
Rurality	Dichotomous	RPDB, OCR	Urban/Rural
Co-morbidity	Categorical	OHIP, CIHI-DAD	ADGs<=3 4<=ADGs<=5 6<=ADGs<=7 8<=ADGs<=9 ADGs>=10
Benign Breast Disease History	Dichotomous	CIHI-DAD, OHIP, SDS, NACRS	Yes/No
Physician Factors			
Age	Continuous	IPDB	
Sex	Dichotomous	IPDB	Male Female Missing
Years in Practice	Categorical	IPDB	<=20 21-30 31-40 41+ Missing
Clinical Volume	Continuous	IPDB	
Practice Setting	Categorical	IPDB, CAPE	Non-rostered Practice Rostered Practice Other
Disease Factors			
Histological Grade	Categorical	Collaborative Stage Data	Low Intermediate

Stage	Categorical	Collaborative Stage Data	High Missing Stage 0-I Stage II Stage III-IV Stage UNK/Missing
Usual Health Care Utilization Characteristics			
Frequency of Doctor Visit	Categorical (screen-detected patients)	OHIP, CIHI-DAD,SDS, NACRS	<10 10-19 20-29 30+
	Continuous (symptomatic patients)	OHIP, CIHI-DAD,SDS, NACRS	
Primary Care provider	Dichotomous	CAPE, OHIP	Yes/No
Continuity of Care	Categorical	OHIP, IPDB	Non-User UPC<0.75 UPC>=0.75
Preventive Service Index	Continuous	OHIP	

3.14 Statistical Analysis

Both descriptive and analytical statistical analyses were performed to fulfill study objectives. Objective 1 included the entire breast cancer cohort, while Objectives 2 and 3 split the study subjects into two different cohorts: screen-detected patients and symptomatic patients. As such, separate analyses were performed for each study objective, and all the analyses were performed at the ICES Queen's using the SAS statistical program (Version 9.3, SAS Institute Inc., Cary, North Carolina).

3.14.1 Descriptive Analysis

Separate descriptive statistics were generated to understand baseline characteristics of study subjects. Central tendency of continuous variables were described with mean, standard deviation, median and interquartile range, while categorical variables were described using proportions and frequency tables.

3.14.2 Objective 1

The first objective of this study was to describe the length of the diagnostic interval and DAU coverage at a provincial level, and also describe their geographic variation by county. The length of the diagnostic interval was described using median and inter-quartile range, as the literature suggests that its distribution is positively skewed (4;8;11). The coverage rates of DAUs were described using proportions. Plots were generated to visualize the geographic variation of the diagnostic interval and the DAU coverage rates. A Pearson Correlation Coefficient was computed for the association between DAU coverage and diagnostic interval with a p-value computed to test the hypothesized inverse correlation against zero.

3.14.3 Objective 2 & 3

Study Objective 2 was to examine the association between DAU use and the length of the diagnostic interval in breast cancer patients whose disease was detected by screening, while Objective 3 was to examine the same association but in the symptomatic cohort. We conducted two separate analyses using the same strategy as described below.

Bivariate associations between covariates and DAU use were examined. This enabled us to assess the degree to which the DAU assignment was balanced (providing evidence for interpretation of results as coming from a natural experiment) and to understand the variation in DAU use. A two-independent-sample t-test or a Wilcoxon rank sum test was used to compare continuous variables between the DAU and the UC groups. An independent chi-square test was used to compare proportions of categorical variables between the DAU and the UC groups.

The bivariate associations between the length of the diagnostic interval and the study covariates were examined through the use of median regression, which is a specific form of quantile regression that models the conditional-quantiles of the response variable (228). The median regression modeling was chosen because it best fits the data properties and provides

robust statistical estimates (229). In addition, results from the median regression retain the original scale and thus are more interpretable to decision-makers for knowledge transfer purposes.

The linearity assumption for continuous variables was assessed using bivariate median regression to decide if categorization was needed (see Appendix D). We chose categories for the continuous variables that considered the size of the interval and the frequency of observations within each interval. Variables were kept as continuous if the linearity assumption was satisfied. Otherwise, a categorical form was used.

A single-level multivariate regression model was used to investigate the association between DAU use and the diagnostic interval while adjusting for confounders. Although one may expect that the data were hierarchical and were clustered at the referring physician level, in fact they were not as the chance of one primary care physician seeing multiple breast cancer patients in one year is very small (230). Confounder selection was not performed in this study because we had sufficient statistical power to control for all possible confounders. Besides, the traditional change-in-estimate method for confounder selection was difficult to use as we had quite a few possible confounders. Therefore, all potential confounders that we previously described were included in the multivariate regression analyses. Multivariate logistic regressions were also performed to assess the success of DAUs in meeting recommended timeliness targets compared to usual care.

3.14.4 Minimum Detectable Effect

The minimum detectable effect calculation based on non-parametric rank-sum tests was not well studied in the literature and there was no way to calculate minimum detectable median differences (231;232). An alternative way was to estimate a minimum detectable effect based on the log-transformed linear regression. The following assumptions informed by cancer registry data (233) and previous studies (28;55;94) were used in the calculation. 1) sample sizes were estimated as 2017 for the screen-detected cohort and 6299 for the symptomatic cohort; 2) the

DAU coverage rate was estimated as 40%; 3) The standard deviation of log-transformed diagnostic delay was estimated as1.07 (11); 4) The alpha is set as 0.05 with a statistical power set as 80% and 5) a 10% confounding adjustment of sample size inflation was taken into account. Therefore, the minimum detectable differences in log-transformed diagnosis interval were 1.09 for screen-detected and 1.05 days for symptomatic patients. Such differences could be interpreted as 1.97 times and 1.85 times relative change in the length of the diagnostic interval, respectively.

Additional calculations were performed for symptomatic patients using a range of DAU coverage rates, as the DAU coverage estimate was based on previous evidence from the screening population (28). Results showed that the estimated minimum detectable effects for symptomatic patients were stable to changes in the DAU coverage rate.

3.15 Ethics Considerations

This research proposal was approved by the Health Sciences Research Ethics Board at Queen's University (see Appendix E) and was also approved by the Institute for Clinical Evaluative Sciences, Cancer Care Ontario (CCO) to access the necessary data. The student received privacy training and signed the confidential agreement before having access to ICES data holdings. With the exception of geo-coded information, all the databases were linked at individual level using an anonymous ICES Key Number (IKN), which eliminates any possibility of identifying individual patients. Confidentiality was maintained through policies and processes in place at ICES Queen's.

Chapter 4

Breast Cancer Diagnostic Interval and Use of Specialized Diagnostic Assessment Units in Ontario, Canada

4.1 Abstract

Background: The amount of time that it takes to reach a breast cancer diagnosis is very important to patients. Ontario breast Diagnostic Assessment Units (DAUs) are designed to improve the quality and timeliness of care during a breast cancer diagnosis. This study described breast cancer diagnostic intervals and DAU use in Ontario, Canada.

Methods: This was a retrospective population-based cohort study of 6898 women with invasive breast cancer diagnosed between Jan 1st, 2011 and December 31st, 2011. Study data sources included administrative databases available at the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario (CCO). The diagnostic interval was defined as the time from the index contact to the cancer diagnosis. DAU use was determined based on the payment record within the organized screening program as well as the hospital where patients were diagnosed. We described the variation of diagnostic intervals and DAU use by the county in which the patients lived and assessed the correlation of DAU use and the diagnostic interval using the Person Correlation Coefficient.

Results: On average, Ontario breast cancer patients waited 4.6 weeks to be diagnosed. Forty-eight percent were diagnosed in a DAU and fifty-two percent were diagnosed in the usual care route. Sixty-eight percent of breast cancer patients met the 7-week timeliness target, with DAUs having a higher rate than UC (74.6% vs. 62.4%, $p<0.001$). At a county level, the diagnostic interval ranged from two weeks to nine weeks, and the DAU coverage rate ranged from zero to one-hundred percent. The average diagnostic interval was inversely correlated with the DAU coverage rate at the county level (Pearson's $r= -0.36$, $p=0.01$).

Conclusions: We observed considerable variation in breast cancer diagnostic intervals and DAU use in Ontario, Canada. DAU use may have influenced the timeliness of the breast cancer diagnosis.

4.2 Introduction

The diagnostic period in breast cancer is characterized by multiple appointments for diagnostic tests and consultations and it often provokes considerable distress and anxiety for women and their families (104;130-132). A long interval in breast cancer diagnosis has been associated with an advanced cancer stage and lower survival (23). Concerns have been raised about the breast cancer diagnostic interval in Canada since considerable variation in the time to diagnosis was observed within the organized breast cancer screening programs (104). Nevertheless, the length and the geographic pattern of the diagnostic interval for breast cancer patients in Ontario have yet to be described.

The diagnostic assessment units (DAU) is designed to improve the patient experience and diagnostic care services (25). Ontario DAUs consist of Breast Assessment Affiliates (BAA) (26;147) under the Ontario Breast Screening Program and some regionally developed breast assessment centres. In 2011, there were 47 BAAs across the province (148) but it is not known how many breast cancer patients were diagnosed through Ontario DAUs at a provincial level, nor do we know if there is any geographic variation in DAU use across Ontario. In addition, it remains unknown if a higher use of Ontario DAUs is correlated to a shorter diagnostic interval at a county level. Therefore, the purpose of this study was to address these knowledge gaps.

4.3 Methods

4.3.1 Study Population and Data Sources

This study was conducted as part of a larger study of DAU use and the diagnostic interval. We used the Ontario Cancer Registry to identify a cohort of women diagnosed with invasive breast cancer between Jan 1st, 2011 and Dec 31st, 2011 in Ontario, Canada. Inclusion criteria were 1) female sex 2) histologically confirmed invasive breast cancer and 3) a single primary cancer. We excluded patients 1) whose cancer was diagnosed at death certificate only 2) who were living outside of Ontario at the time of diagnosis and 3) who did not have the Ontario Health Insurance

Plan (OHIP) coverage for at least three years prior to the diagnosis. This study was approved by the Health Sciences Research Ethics Board at Queen's University at Kingston, Canada (Appendix E).

Data were obtained from administrative databases at the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario. The Ontario Cancer Registry was used to identify all incident breast cancer cases, the date of diagnosis and the postal code at the time of diagnosis. The length of the diagnostic interval was measured at an individual level using information from the Ontario Breast Screening Program (OBSP) database, the Ontario Health Insurance Plan Claims Database (OHIP), the National Ambulatory Care Reporting System (NACRS), the Canadian Institute for Health Information/ Discharge Abstract Database (CIHI/DAD) and the Same-day Surgery Database (SDS). A list of BAA hospitals was provided to us by the OBSP and a separate list of regional breast assessment centres was obtained through an email survey to Cancer Care Ontario Regional Primary Care Leads and the OBSP Regional Program Managers.

4.3.2 Study Variables

The length of the diagnostic interval was calculated as the time from the index contact to the cancer diagnosis for each individual breast cancer patient. A 12-month look-back time frame for abnormal OBSP screening and a 6-month look-back time window for the rest of breast-related services were determined based on previous studies (114;145;146;189) as well as our own data (see Appendix B). The index contact was ascertained using a strategy that is illustrated in Figure 4-1. We worked backwards from the date of diagnosis to identify various breast-related procedures and physician visits using information obtained from the OHIP, CIHI/DAD, SDS and NACRS databases. The earliest record for each breast-related procedure or visit was identified, and the most recent visit to the referring physician who ordered the earliest diagnostic procedure was further identified. We assigned the index contact date as the earliest screening date (A) if a patient ever had a screening mammogram within defined time period, regardless of the other tests.

The index contact date was assigned using the earliest date among dates (B-F) for patients without a one-year screening history. We also dichotomized the diagnostic interval at 7 weeks in accordance with the Canadian timeliness guideline which recommends that 90% of abnormal screening tests should be resolved within 7 weeks if a tissue biopsy is required (145).

Use of DAU for each individual patient was determined using a hierarchy (see Appendix C): 1) for the OBSP screen-detected patients, the BAA use was ascertained using the OBSP payment records. Among those OBSP screen-detected patients without a BAA payment record, hospitals where a biopsy/surgery was performed closest to the date of diagnosis were compared with the list of regional breast assessment centres to ascertain non-OBSP DAU use; 2) for the rest of the patients, DAU use was determined by comparing diagnosing hospitals with DAU hospitals.

4.3.3 Statistical Method

The length of the diagnostic interval was described using median and inter-quartile range, as the literature suggests that its distribution is positively skewed (4;8;11). The coverage rates of DAUs and the rates of meeting timeliness targets were described using proportions. Kruskal-Wallis test was used to compare diagnostic intervals across counties. Chi-square test was used to compare proportions between the DAU and UC groups. Plots were generated to visualize the geographic variation of the diagnostic interval and DAU coverage rates. Pearson Correlation Coefficient was computed and compared with zero to test the hypothesized inverse correlation.

4.4 Results

Figure 4-2 displays the process of cohort selection. The final sample size was 6898, comprising 2499 (36.2%) screen-detected patients and 4399 (63.8%) symptomatic patients.

The mean age of women was 61.2 (SD: 13.5) and 52% were aged 50 to 69, which corresponds to the targeted age category for the OBSP. Of screen-detected patients, 1986 (79.5%)

were detected through the OBSP and 513 (20.5%) were detected through opportunistic breast screening. The proportion of screen-detected patients by age group is displayed in Table 4-1.

At a provincial level, the median time to diagnosis was 4.6 weeks (32 days), with an interquartile range of 17 to 60 days. Sixty-eight percent of breast cancer patients were diagnosed within 7 weeks, while ten percent waited more than three months (107 days) to get a cancer diagnosed. Overall, 48.4% were diagnosed at a DAU in 2011. The median time to diagnosis was 3.8 weeks (27 days) for DAU patients and 5.3 weeks (37 days) for UC patients. DAUs had a significantly higher rate in achieving the 7-week target than UC (74.6% vs. 62.4%, $p<0.001$).

The descriptive statistics of the diagnostic interval and the DAU coverage rate at a county level are presented in Table 4-2. The median time to diagnosis ranged from 2.1 weeks (15 days) to 9.3 weeks (65 days), and the DAU coverage rate ranged from 0% to 100%. Differences in the length of the diagnostic interval were statistically significant across counties ($p<0.001$). Nineteen (38.8%) of forty-nine counties did not have a DAU. Of these, 11 (57.9%) counties had a median diagnostic interval greater than or equal to the provincial median, and 14 (73.7%) had a DAU coverage rate below the provincial DAU coverage rate.

Figure 4-3 and Figure 4-4 present plots of the length of the diagnostic interval and DAU coverage rates across Ontario counties. A scatter plot between the DAU coverage rate and the diagnostic interval is presented in Figure 4-5, with the size of the bubble representing the number of patients at each county. As we expected, the average diagnostic interval was inversely correlated with the DAU coverage rate at the county level (Pearson's $r= -0.36$, $p=0.01$).

4.5 Discussion

Breast cancer remains a public health concern in Ontario, with at least 8720 incident cases diagnosed in Ontario during 2011. Overall, thirty-six percent of breast cancer patients were initially detected by screening, comparable to a forty-four percent reported in Quebec (11) and a thirty-three percent reported among low-income women in California, the United States (31). The

low overall screen-detection rates may be due to the specified age-eligibility criteria for screening in the organized programs. Both Ontario and Quebec breast screening programs target women aged 50 to 69, while the California program targets low-income women aged above 40 (234). Specifically for the screen-target age group (50-69 years old), a total of 48.4% breast cancer patients were detected by screening. Of these, 88% were detected by the OBSP, which is much higher than a 63% in age-eligible Ontario women screened between 2007 and 2008 (55). This discrepancy might be attributed to the newly introduced OHIP code that we used to identify OHIP screening, as we could have missed some OHIP screening mammograms that were miscoded as diagnostic. Another possible explanation might be the different breast cancer risks between women who participated in the OBSP and those who received opportunistic screening.

The median time to breast cancer diagnosis was 4.6 weeks in Ontario. This was shorter than a median of 5.6 weeks in screen-detected patients reported from Canadian organized breast screening programs (104). This improvement was largely driven by the DAU patients (median=3.8 weeks) while the patients in UC continued to wait an average of 5.3 weeks to be diagnosed. Overall, 68.3% of breast cancer patients were diagnosed within 7 weeks, which was similar to a 64% rate reported in women with abnormal OBSP screening tests during 2010 (235). DAUs were more successful in meeting the recommended timeliness target compared to UC. However, both fell short of the 90% goal (145). Of particular concern is the finding that 10% of breast cancer patients waited more than three months to reach a cancer diagnosis, as sufficient evidence suggests that a delay of more than 3 months can lead to lower survival (23).

Considerable geographic variation in the length of the diagnostic interval and DAU use among breast cancer patients was for the first time reported across Ontario counties. The median time to diagnosis ranged from 2.1 weeks in the Prince Edward Division and the Renfrew County to 9.2 weeks in the Muskoka District Municipality. The DAU coverage rate ranged from 0% in the Muskoka District Municipality to 100% in the Lennox and Addington County and also the

Perth County. Of our interest is the finding that counties without a DAU did not always have a low DAU coverage rate or a long diagnostic interval. We think this is because DAU hospitals that were located close to county boundaries can serve patients from multiple counties, and thus a county might not best represent DAUs' catchment area. Despite this, we observed an inverse association between the length of the diagnostic interval and the DAU coverage rate at a county level. This provides ecological evidence for the hypothesis that DAUs might be effective in shortening diagnostic intervals for breast cancer patients. Further research examining the hypothesized timeliness benefits of DAUs is warranted.

This study has some limitations. Firstly, our study results only apply to a subset of patients who had breast cancer. Evidence suggests that women with invasive breast cancer get a quicker diagnosis compared to those with benign diseases (45;164). So we expect a longer diagnostic interval for patients with benign breast diseases. We could not estimate the DAU coverage rates for patients with benign breast abnormalities. Secondly, we did not have test results using administrative databases and we had to assume that an OHIP screening within 6 months before diagnosis was abnormal. Some symptomatic patients who had negative OHIP screening tests might have been misclassified as screen-detected, while a small proportion (less than 5%) of screen-detected patients whose abnormal screening was earlier than 6 month before diagnosis might have been misclassified as symptomatic (see Appendix B). Although this could have biased the point estimates of the diagnostic interval and screen-detection rate in either direction, we think that the amount of influence on our results is small. Thirdly, the most recent visit to the referring doctor prior to the earliest diagnostic procedure might not have been the visit in which the test referral occurred. The actual referring encounter might have occurred earlier so our choice led to a conservative estimate of the diagnostic interval in those cases. Fourthly, the accuracy of the use of the screening mammogram code in OHIP is unknown as it was introduced in late 2010. So some screening mammograms might have been billed as diagnostic and thus we

might have underestimated the proportion of screen-detected patients. We expect this influence to be small, because the frequency of use of this new code increased dramatically during the first three months of its introduction and had leveled off by the time of this study indicating its use had been adopted by Ontario physicians (236). Lastly, the determination of DAU use was subject to misclassification (see Appendix C) and might have decreased the accuracy of point estimates.

This study also has several strengths. This is the first study providing information on the length of the diagnostic interval and its geographic variation at a population-level for breast cancer patients in Ontario. This study also for the first time filled the knowledge gap in the overall DAU use and its geographic patterns in Ontario. This provides baseline evidence for future system evaluation and health policy making. Further research is warranted to confirm the observed ecological association between DAU use and the length of the diagnostic interval in breast cancer patients.

4.6 Acknowledgements

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Table 4-1: Proportion of screen-detected breast cancer patients by age group

Age groups	*Screen-detected*			*Symptomatic*
	OBSP screen	OHIP screen	Total (%)	Total (%)
Overall	1986-1990	509-513	2499 (36.2)	4399 (63.8)
<50 years	<6	153-157	158 (11.1)	1270 (88.9)
50-69 years	1527	209	1736 (48.4)	1851(51.6)
>69 years	458	147	605 (32.1)	1278 (67.9)

Cells with a count less than 10 were suppressed due to ICES privacy regulations

Table 4-2: Descriptive statistics of diagnostic interval and DAU coverage at a county level

County (MOH code)	*N*	*Diagnostic Interval Median (IQR)*	*DAU Coverage rate (95% CI)*
Brant County† (1)	60	31 (16.5-49.5)	6.6 (0.4, 13.0)
Bruce County†(2)	46	22 (15-44)	73.9 (61.2, 86.6)
Dufferin County† (3)	30	46.5 (27-64)	6.7 (-2.3, 15.59)
Elgin County† (4)	59	49 (33-83)	18.6 (8.7, 28.6)
Essex County (5)	251	25 (14-45)	85.7 (81.3, 90.0)
Frontenac County (6)	89	21 (14-32)	98.9(96.7, 101.1)
Grey County (7)	63	30 (18-54)	76.2 (65.7, 86.7)
Haldimand-Norfolk Regional Municipality† (8)	68	37.5 (21.5-76)	17.6 (8.6, 26.7)
Haliburton County† (9)	*	*	*
Halton Regional Municipality† (10)	215	36 (17-62)	26.0(20.2, 31.9)
Hastings County (11)	89	22 (16-58)	96.6 (92.9, 100.4)
Huron County† (12)	36	30 (16-57.5)	88.9 (78.6, 99.2)
Chatham-Kent Division (13)	62	40.5 (27-74)	91.9 (85.2, 98.7)
Lambton County (14)	98	25.5 (10-55)	64.3 (54.8, 73.8)
Lanark County† (15)	41	38 (26-50)	53.7 (38.4, 68.9)
Leeds and Grenville United Counties (16)	68	31.5 (22-47)	86.8 (78.7, 94.8)
Lennox and Addington County† (17)	19	27 (10-55)	100 (100.0, 100.0)
Toronto Division (18)	1289	38 (22-67)	25.52 (23.1, 27.9)
Middlesex County (19)	285	42 (17-70)	94.0 (91.3, 96.8)
Muskoka District Municipality† (20)	49	65 (30-108)	0 (0.0, 0.0)
Niagara Regional Municipality (21)	241	35 (22-63)	90.9 (87.2, 94.5)
Northumberland County (23)	57	20 (12-44)	94.7 (88.9, 100.5)
Durham Regional Municipality (24)	283	33 (17-59)	54.1 (48.3, 59.9)
Ottawa Division (25)	549	28 (15-51)	74.7 (71.0, 78.3)
Oxford County (26)	62	16.5 (8-42)	85.5 (76.7, 94.3)
Peel Regional Municipality (27)	567	37 (22-66)	27.5 (23.8, 31.2)
Perth County (28)	43	23 (15-41)	100 (100.0, 100.0)
Peterborough County (29)	73	20 (9-39)	41.1 (29.8, 52.4)
Prescott and Russell United Counties (30)	52	49 (28-82)	48.1 (34.5, 61.7)
Prince Edward Division (31)	19	15 (8-29)	94.7 (84.7, 104.8)
Renfrew County (32)	51	15 (8-44)	90.2 (82.0, 98.4)
Simcoe County (33)	245	24 (11-62)	4.1 (1.6, 6.6)
Stormont, Dundas and Glengarry United Counties (34)	74	41 (25-73)	36.5 (25.5, 47.5)
Kawartha Lakes Division (35)	45	23 (10-49)	28.9 (15.6, 42.1)
Waterloo Regional Municipality (36)	281	30 (18-57)	61.9 (56.2, 67.6)
Wellington County† (37)	94	32 (21-52)	19.1 (11.2, 27.1)
Hamilton Division (38)	266	19.5 (11-36)	41.0 (35.1, 46.9)
York Regional Municipality (39)	528	32 (18-57)	23.9 (20.2, 27.5)
Algoma District (40)	68	24 (14-45.5)	88.2 (80.6, 95.9)
Cochrane District (41)	42	34.5 (27-55)	38.1 (23.4, 52.8)
Kenora District† (42)	31	50 (21-71)	41.9 (24.6, 59.3)
Manitoulin District† (43)	14	19.5 (9-28)	50.0 (23.8, 76.2)
Nipissing District† (44)	53	22 (15-37)	13.2 (4.1, 22.3)
Parry Sound District† (45)	28	32.5 (16-60.5)	17.9 (3.7, 32.0)
Rainy River District† (46)	*	*	*
Greater Sudbury Division (47)	87	24 (10-47)	46.0 (35.5, 56.4)
Sudbury District† (48)	15	22 (16-49)	40.0 (15.2, 64.8)
Thunder Bay District (49)	84	40 (26-67.5)	97.6 (94.4, 100.9)
Timiskaming District† (50)	11	53 (33-97)	36.4 (7.9, 64.8)

* Cells with counts less than 10 were suppressed due to ICES privacy regulations.

† Counties without a DAU

Figure 4-1: Measurement of the diagnostic interval

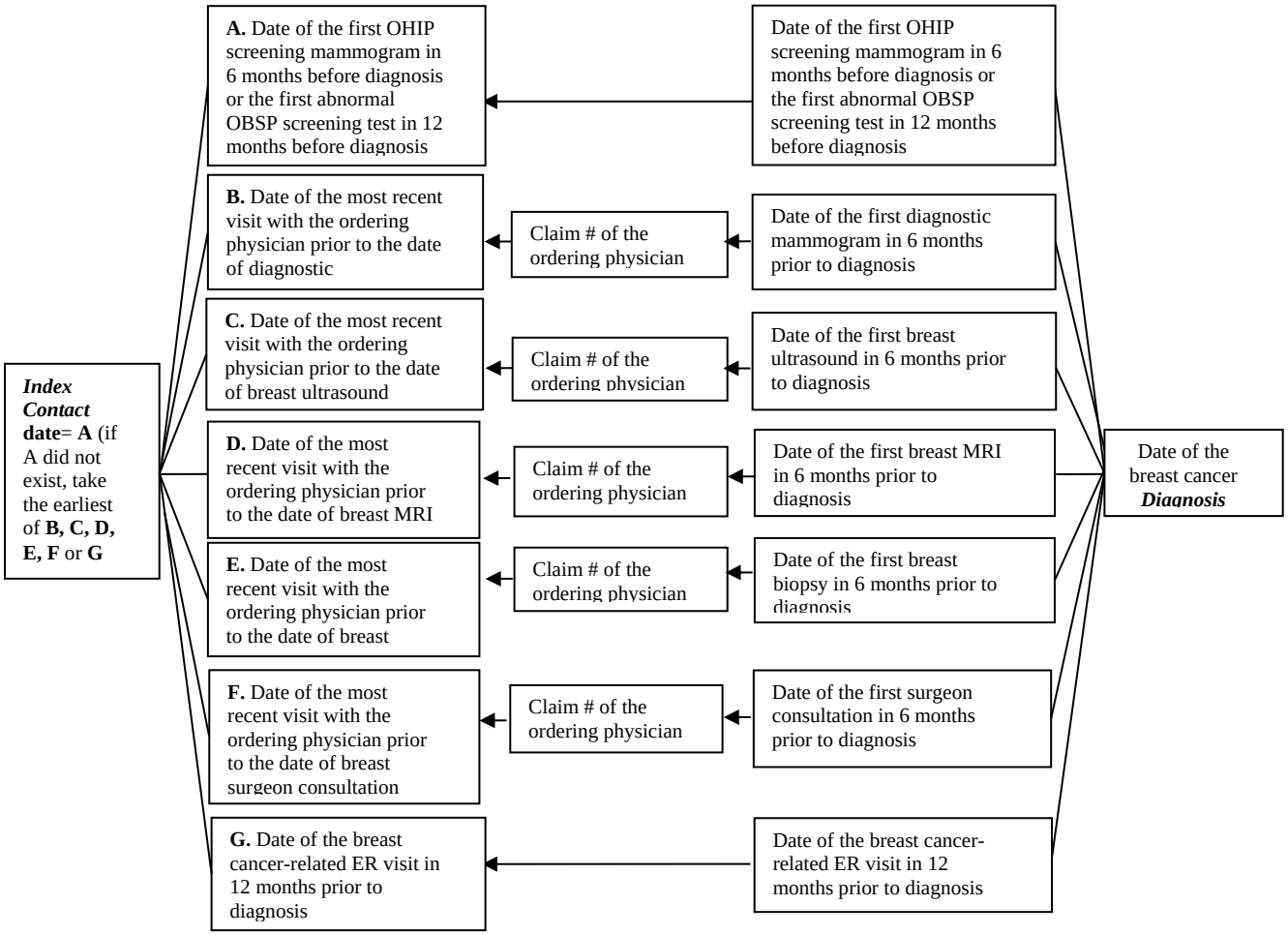


Figure 4-2: Flow chart of the cohort selection

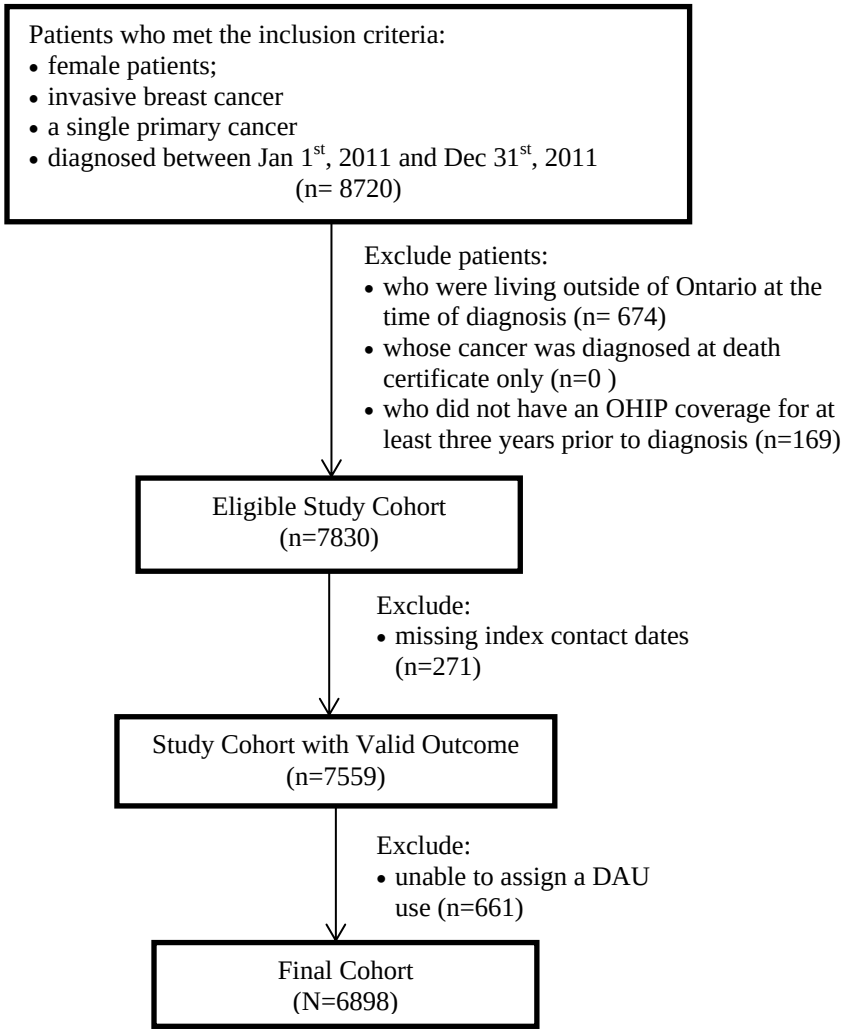
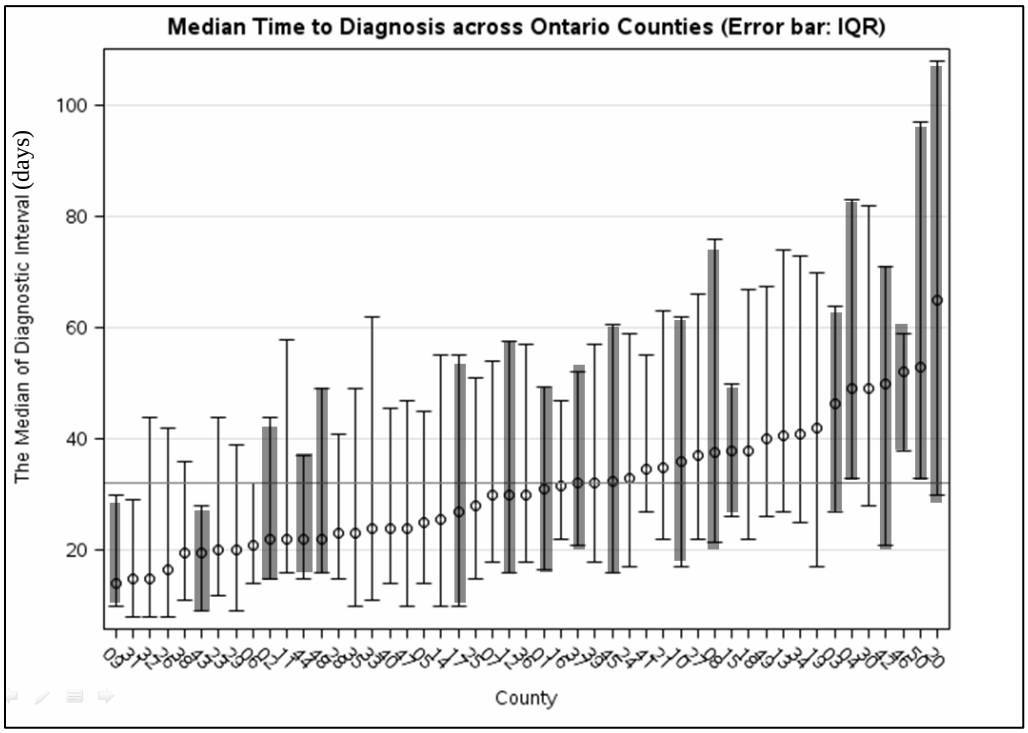


Figure 4-3: Median diagnostic interval for breast cancer patients by Ontario county (N=6898)



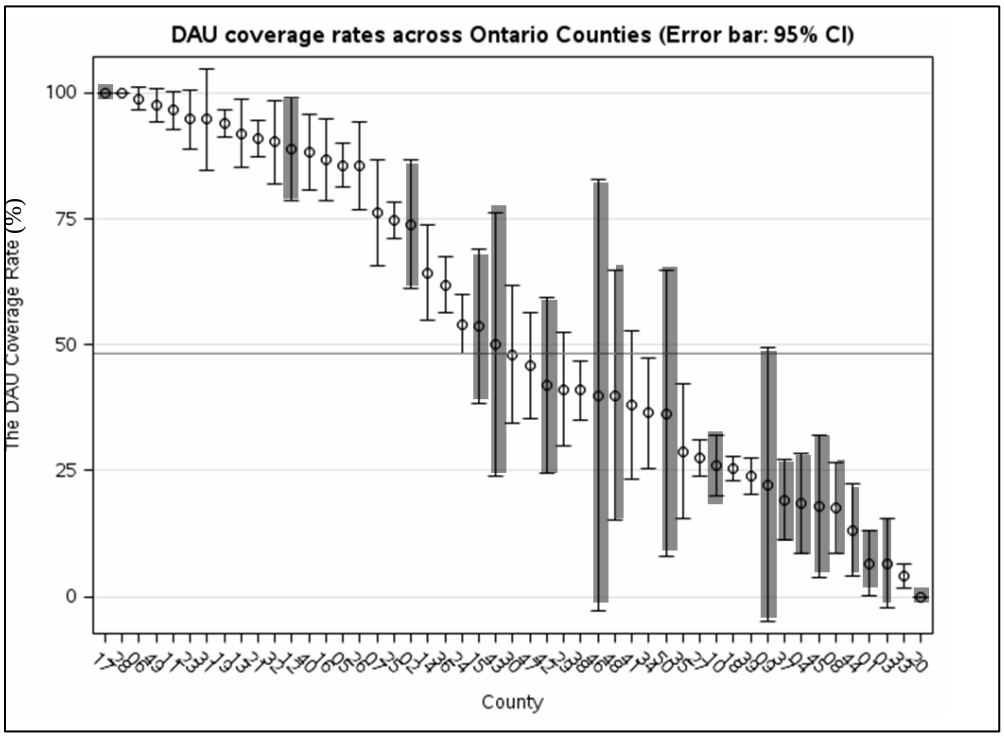
The county name for each county number is shown in Table 4-2

The error bar represents the interquartile range of the diagnostic interval

The reference line represents the provincial median diagnostic interval (32 days)

Counties without a DAU were highlighted in gray

Figure 4-4: DAU coverage rates by Ontario county (N=6898)



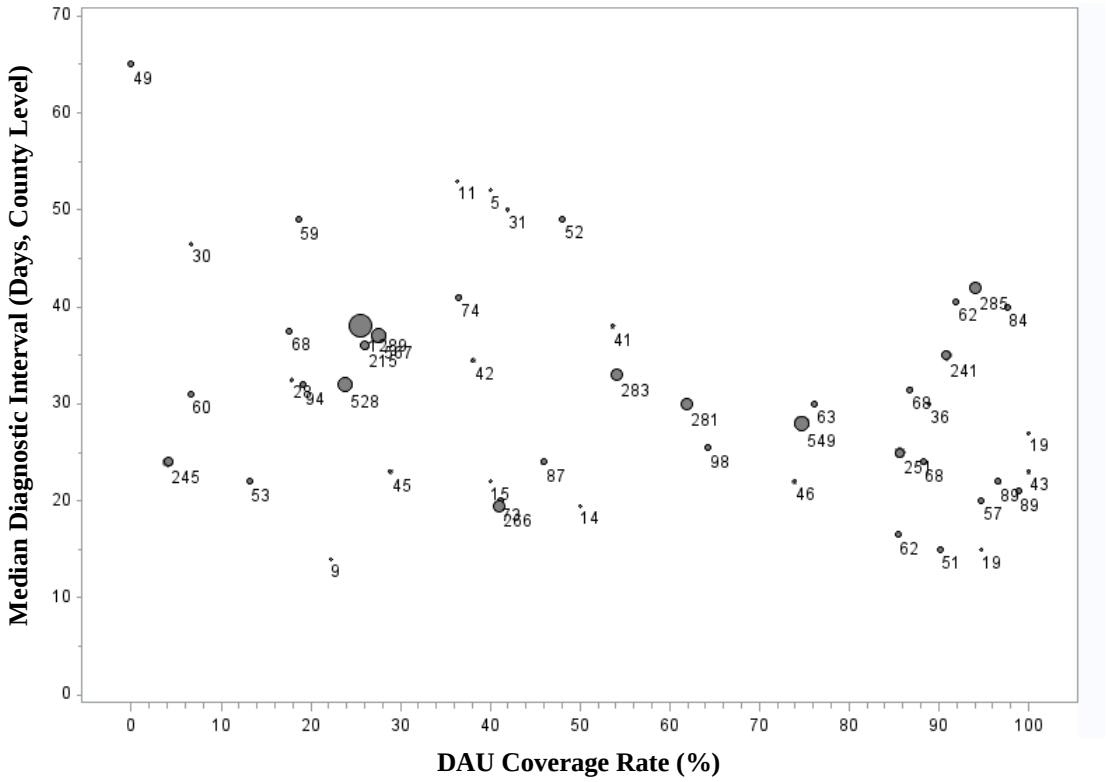
The county name for each county number is shown in Table 4-2

The error bar represents the 95% confidence interval of the DAU coverage rate

The reference line represents the overall DAU coverage rate (48%) at a provincial level

Counties without a DAU were highlighted in gray

Figure 4-5: Bubble plot of the association between the diagnostic interval and DAU coverage by Ontario county (N=6898)



Chapter 5

A Population-Based Study of the Effect of a Specialized Diagnostic Unit on the Diagnostic Interval in Screen-detected Breast Cancer Patients

5.1 Abstract

Background: The diagnostic assessment unit (DAU) is an organizational structure designed to provide a seamless transition from abnormality detection to definitive diagnosis. Ontario DAUs are comprised of Breast Assessment Affiliates (BAA) and regional breast assessment centres. The purpose of this study was to examine the length of the diagnostic interval for breast cancer patients diagnosed at a diagnostic assessment unit versus those diagnosed through usual care.

Methods: This was a retrospective population-based cohort study of 2499 women with screen-detected breast cancer diagnosed between Jan 1st, 2011 and December 31st, 2011. Study data sources included administrative databases available at the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario (CCO). The diagnostic interval was defined as the time from an abnormal screening test to the cancer diagnosis. DAU use was determined based on the payment records within the organized screening program as well as the hospital where patients were diagnosed. Multivariate median regression was used to control for possible confounders of the association between DAU use and the length of the diagnostic interval.

Results: Overall, the median time to diagnosis was 29 days. Fifty-one percent were diagnosed in a DAU and forty-nine percent were diagnosed in the usual care route. DAUs had a higher rate in achieving the Canadian timeliness targets compared to usual care (79.1% vs. 70.2%, $p<0.001$). Compared to usual care, a DAU reduced the time to diagnosis by 9 days (95% CI: 6.4-11.6). This effect was reduced to 8.3 days after adjusting for patient demographics, disease characteristics and patients' usual health utilization characteristics.

Conclusions: In addition to providing high-quality and coordinated care, we have demonstrated that DAU use was significantly associated with improved timeliness of abnormal screening follow-up for Ontario breast cancer patients when compared to those diagnosed through the usual care route. Although an 8.3-day reduction in the time to diagnosis may not affect clinical outcomes, it might reduce patient anxiety and distress associated with the diagnostic interval.

5.2 Introduction

Breast cancer screening has been considered the most important strategy to achieve an early diagnosis and reduce breast cancer mortality rates (55;85;86). The benefits of breast cancer screening, to a large extent, depend on the timely diagnosis and initiation of treatment once an abnormality is detected (9). In Canada, concerns have been raised about the timeliness of diagnostic follow-up after abnormal screening tests. A Working Group on the Integration of Screening and Diagnosis reported the median time to diagnosis was over six weeks where a core biopsy or an open biopsy was performed (142). In addition, approximately 10% of patients waited 12 weeks or longer to receive a cancer diagnosis (142). Delayed diagnosis has been associated with patient anxiety, disrupted daily function and adverse clinical outcomes (6;20-23). Thus, a seamless transition between an abnormal screening test and diagnosis should be achieved.

In 2004, the Ontario Breast Screening Program (OBSP) introduced the Breast Assessment Affiliates (BAA) to reduce the time to diagnosis after abnormal screening tests (26). In contrast to the usual care system (UC) where diagnostic assessments were arranged by family doctors (28;104;131), BAAs centralize the provision of care using a multidisciplinary team that contains a patient navigator who coordinates diagnostic tests. BAAs also ensure the delivery of high-quality diagnostic services by applying professional standards and organizational threshold criteria (26;27). Apart from BAAs, Ontario has some regional breast assessment centres that were independently developed to expedite the diagnostic process. Both BAAs and regional breast assessment centres were referred to as diagnostic assessment units (DAU) in this study, as they share the same goal and are likely to have similar organizational components.

The literature contains little evidence on the population-level influence of Ontario DAUs on the timeliness of the breast cancer diagnosis. One retrospective study suggested BAAs are more successful in achieving timeliness targets than the usual care system for patients with abnormal screening results seen in the Ontario Breast Screening Program (OBSP) (28). We do

not know how much quicker the DAU diagnostic process is compared to the usual care system at the population level. The purpose of this study was to compare the time to diagnosis after abnormal screening tests among Ontarian breast cancer patients who were diagnosed through DAUs versus those diagnosed through UC.

5.3 Methods

5.3.1 Study Design and Study Population

We conducted a population-based retrospective study among a cohort of breast cancer patients diagnosed between Jan 1st, 2011 and Dec 31st, 2011 in Ontario, Canada, who had cancer detected by breast screening tests. Breast cancer patients were considered screen-detected if patients ever had an abnormal OBSP screening test within 12 months prior to diagnosis or a screening mammogram from public fee-for-service sector (opportunistic screening) within 6 months prior to diagnosis.

We used the Ontario Cancer Registry (OCR) to identify all female patients in Ontario diagnosed with invasive breast cancer (ICD-9 codes: 174.0 to 174.9) between Jan 1st, 2011 and December 31st, 2011. Inclusion criteria were: 1) female sex 2) histologically confirmed invasive breast cancer and 3) single primary cancer. Among eligible patients identified from the OCR, we excluded patient 1) whose cancer was diagnosed at death certificate only 2) who was living outside of Ontario at the time of diagnosis and 3) who did not have the Ontario Health Insurance Plan (OHIP) coverage for at least three years prior to the diagnosis for the purpose of measuring patients' usual health care utilization patterns 4) whose breast cancer was not screen-detected. This study was approved by the Health Sciences Research Ethics Board at Queen's University at Kingston, Canada (see Appendix E).

5.3.2 Data Sources

We used ten population-based administrative databases from the Canadian province of Ontario to identify the study cohort and derive study variables. With the exception of geo-coded data, all the databases were linkable at an individual level using an anonymous key number. We used the OCR to identify the study cohort and determine the date of diagnosis. Breast cancer patients were ascertained as screen-detected using the Ontario Breast Screening Program database combined with the Ontario Health Insurance Plan Claims Database (OHIP), which contains all claims made by physicians (and other health care providers) for insured services provided to the residents of the province. The OHIP was also used in combination with the National Ambulatory Care Reporting System (NACRS), the Canadian Institute for Health Information/ Discharge Abstract Database (CIHI/DAD) and the Same-day Surgery Database (SDS) to identify all breast-related services, the associated dates and physicians, diagnostic institutions, past disease history, and the usual health care utilization. Patients' demographics (including date of birth, sex, postal codes) and OHIP coverage status were obtained from the Registered Persons Database (RPDB). Physician's characteristics were assessed using information from the Institute for Clinical Evaluative Sciences (ICES) Physician Database combined with the Client Agency Program Enrollment Data. The Collaborative Stage Data, which collected a comprehensive range of data items from clinical medical records and pathological reports using a Collaborative Stage Data Collection System (181-184), was used to determine cancer staging (including tumor size) and the histological grade of cancer. A list of BAA hospitals was provided to us by the OBSP and a separate list of regional breast assessment centres was obtained through an email survey to Cancer Care Ontario Regional Primary Care Leads and the OBSP Regional Program Managers.

5.3.3 Study Variables

Our outcome was the diagnostic interval, which was defined as the time from the initial screening test to the date of diagnosis. Initial screening test was identified as the earliest abnormal

OBSP screening test within 12 months before diagnosis or the earliest OHIP screening mammogram (OHIP fee codes= X172, X178) within 6 months before diagnosis, whichever occurred first (see Appendix B). The date of diagnosis was ascertained from the Ontario Cancer Registry database, with its accuracy previously demonstrated in a validation study (178). The diagnostic interval was also dichotomized at 7 weeks in accordance with the recently updated Canadian timeliness targets for the abnormal screen follow-up (145).

We determined DAU use separately for the OBSP screen-detected patients and opportunistic screen-detected patients, as the OBSP has its own database tracking BAA assessment records for payment purposes. For breast cancer patients whose initial screening was received within the OBSP, they were diagnosed through a DAU if 1) the OBSP database indicated a BAA payment record or 2) they had a biopsy/surgery performed at a regional breast assessment centre. Otherwise, they were diagnosed through the usual care (UC). DAU use for patients detected through opportunistic screening was assigned by comparing the biopsy/surgery hospital with two lists of DAU (BAAs and regional assessment centres) hospitals (Appendix C).

Variables we examined for potential influences on the association between DAU use and the diagnostic interval were organized as

***1) patient characteristics*:** age, recent immigration status (Yes/No), socio-economic status based on area-level material deprivation index (195;196), urban/rural residence based on Rurality Index for Ontario 2008 (RIO2008) scores (198) (Yes/No), co-morbidity based on the Johns Hopkins Aggregated Diagnosis Groups (ADGs) (201), and benign breast disease history (Yes/No)

2) disease characteristics: histological grade of cancer based on Nottingham Grading System (237;238) (low/medium/high) and cancer stage based on American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Tumor-Node-Metastasis staging (181;182).

3) usual health care utilization characteristics were assessed between 36 months and 12 months prior to the date of diagnosis, as evidence suggests that a two-year look back period provides stable estimates of usual health care utilization (166). Factors examined included: frequency of doctor visits, primary care provider (Yes/No), continuity of care based on Usual Provider Continuity (UPC) index (223) (High/Low/Non-user) and preventive services index (166), which was calculated as the as proportion of preventive services used out of the total number of preventive services for which an individual was eligible.

5.3.4 Statistical Analysis

Descriptive statistics were generated to understand characteristics of the study subjects. The distribution of study covariates was described and compared between DAU and UC. We conducted median regressions (228) to examine bivariate associations between covariates and the diagnostic interval, as the literature shows the distribution of the length of the diagnostic interval is positively skewed (4;8;11). We also conducted multivariate median regressions to assess the association between DAU use and the length of the diagnostic interval, controlling for all other study covariates. Logistic regressions were used to assess the success of DAUs in meeting recommended timeliness targets. A sensitivity analysis was performed by excluding regional breast assessment centres from DAUs to understand possible differences between BAAs and regional breast assessment centres. Both descriptive and analytical statistical analyses were performed at the ICES Queen's Health Services Research Facility using SAS statistical Program (Version 9.3, SAS Institute Inc., Cary, North Carolina).

5.4 Results

We identified 8720 patients who met the inclusion criteria with a diagnosis of breast cancer between Jan 1st, 2011 and Dec 31st, 2011 from the Ontario Cancer Registry. Of these, we excluded 647 patients who were living outside of Ontario at the time of diagnosis, zero patient who was diagnosed at the death certificate only and 169 patients who did not have OHIP

coverage for at least three years prior to diagnosis. 5278 patients who were not screen-detected are the subject of a separate report on the diagnostic process for symptomatic patients. We further excluded 53 patients whose DAU use (yes/no) was not available. The final study sample size was 2499, including 1986 (79.5%) patients detected by the OBSP screening and 566 (22.7%) detected by opportunistic breast screening.

Characteristics of the study population are shown in Table 5-1. The mean age of the study population was 63 years and more than 90% of patients were aged above 50. Patients diagnosed at DAUs were slightly older than those in the usual care route (UC), although the difference was not statistically significant. Patients diagnosed at DAUs were slightly more likely to live in a rural area (11.7% vs. 8.2%, p=0.004) than those in UC.

Table 5-2 and Table 5-3 display disease characteristics and usual health care utilization characteristics of study subjects, respectively. Over 90% of screened breast cancer was diagnosed at early stages (stage 0-II), with a higher proportion of stage III-IV cancer seen in UC than in the DAUs (p=0.03). The proportion of patients who had a primary care provider was lower in the DAU group than in UC (p=0.02). Patients diagnosed at DAUs were less likely to get an annual physical exam (33.9% vs. 37.9%, p=0.04) and they were more likely to get a breast screening test (70.6% vs. 66.8%, p=0.08) compared to those in UC.

The diagnostic timeliness by DAU use is displayed in Table 5-4. Overall, the median time to diagnosis was 29 days with an interquartile range of 17 to 50 days. Ten percent of patients waited more than 11 weeks (79 days) before a cancer diagnosis. Approximately half (51.4%) of breast cancer patients attended a DAU for their diagnostic assessments. Breast cancer patients diagnosed at DAUs were more likely to have an abnormal screening resolved within 7 weeks than those in UC (79.1% vs. 70.2%, p<0.001). Patients who met the 7-week target were more likely to use DAUs (vs. UC) than those who did not (OR: 1.6, 95% CI: 1.3-1.9). The odds ratio increased slightly to 1.65 (95% CI: 1.4-2.0) after adjusting for covariates.

Table 5-5 summarizes results of bivariate and multivariate analyses through the use of median regressions. The average time to diagnostic resolution was 9 days shorter for patients at DAUs than those in UC ($p<0.001$). Age between 70 and 79 years (vs. age 60-69) and Stage 0-I (vs. Stage III/IV) were significant predictors for a longer diagnostic interval ($p=0.01$ and $p<0.001$, respectively). Multivariate analyses reduced the effect of DAUs to 8.3 days and Stage II (vs. Stage III/IV) became a significant predictor for a longer diagnostic interval ($p<0.001$ and $p=0.05$, respectively). Age above 80 years (vs. age 60-69) and having a history of benign breast disease was marginally associated with the diagnostic interval after controlling for all the other variables ($p=0.08$ and $p=0.05$, respectively).

A sensitivity analysis found similar results when we restricted to BAA use, with an unadjusted effect estimate of 9 days shorter than UC and an adjusted effect estimate of 8.2 days.

5.5 Discussion

This study provides population-level information on the use of Ontario DAUs for breast cancer patients whose disease was detected by screening. Overall, we found that 51.4% of patients were diagnosed in a DAU and 48.6% were diagnosed in UC. Patient demographics, disease characteristics, and usual care utilization characteristics were similar between the DAU and UC groups, although small differences were statistically significant due to the large sample size. We expect that being diagnosed in a DAU was largely determined by where the woman lived rather than clinical presentations or demographic characteristics because DAUs did not yet cover every region of the province in 2011. Thus, this study can be considered as a natural experiment assessing the relative timeliness of DAUs compared to UC.

To the best of our knowledge, this is the first population-based study in Ontario describing and examining the timeliness of abnormal screening follow-up and its association with DAUs for breast cancer patients. We found a median diagnostic interval of 4.1 weeks, which was considerably shorter than a median of 5.6 weeks reported from seven provincial breast screening

programs in 1996 (104) and a median of 5.9 weeks reported in the organized screening program of Quebec between 2002 and 2003 (11). This overall improvement is largely confined to the DAU group (at 3.7 weeks), as the UC group continues to take 5 weeks to be diagnosed.

On average, patients in DAUs waited 9 days shorter before the diagnosis compared to those in UC. This difference did not materially change (8.3 days) after adjusting for all potential confounders. Our finding was consistent with previous evidence from two before-and-after studies that suggested timeliness benefits of DAUs in Ontario, with one reporting a considerable time reduction (53%) between cancer suspicion and diagnosis (from 42 days to 20 days) (151) and the other reporting significant decreases in all time intervals studied (150). The magnitude of time reduction (22 days) associated with a regional DAU was higher than we observed in this study. We attributed this discrepancy to the organizational variation of DAUs, as DAUs are flexible to decide the most appropriate care model based on local contexts and resources given they met the organizational threshold criteria (24;28). An alternative explanation may be the differences in study methodology. No contemporaneous comparison group was used and no other variables were controlled for in previous studies (151), and their small sample size (n=76) may have decreased the accuracy of their estimates.

Breast cancer patients diagnosed at DAUs were more likely to have an abnormal screening resolved within 7 weeks than those in UC (79.1% vs. 70.2%), which agrees with previous finding that DAUs are more successful in meeting the 7-week target (when an open biopsy was required) than UC for OBSP patients with or without cancer (59.9% vs. 50.6%) (28). This study observed a higher proportion of breast cancer patients who met the Canadian targets, and this might be because we restricted the study subjects to breast cancer patients. Many studies have demonstrated that women with invasive breast cancer get a quicker diagnosis compared to those with benign diseases (45;164). Additionally, patients diagnosed within 7 weeks were 1.8

times more likely to use DAUs than UC compared to patients diagnosed beyond 7 weeks, indicating that DAUs had a better performance in achieving the timeliness targets.

Improved timeliness of diagnostic follow-up for breast cancer patients in DAUs may be attributed to its organizational components of an interdisciplinary team, a patient navigator and a mechanism of direct referral (27). An interdisciplinary model of care has been consistently associated with shorter diagnostic waiting times in the literature (149), with one study reporting an average time reduction of 26.5 weeks (161). Having a patient navigator at a DAU who is responsible for coordinating diagnostic care and providing patient support (27) may contribute to a rapid diagnosis (163;239-241). Evidence suggests that a direct referral can reduce the time to diagnostic resolution (164;165). So the expedited diagnostic work-up in a DAU might also be due to the fact that DAUs organize additional investigations without re-referrals from the primary care physician (28). Other features of DAUs such as ensured availability of resources, diagnostic equipment and high levels of clinical expertise may also explain the observed effect (27). Results of a sensitivity analysis showed no difference in the magnitude of effect when regional breast assessment centres were excluded from DAUs (8.2 days vs. 8.3 days), indicating the two types of DAUs are similarly effective.

Patients between 70 and 79 years of age waited four days longer (vs. 60 to 69). This result is not consistent with the literature where most studies reported non-significant results based on age. This inconsistency may be due to different methods for modeling age where some studies have treated age as continuous (4) while others have dichotomized age at 50 years (34). We saw no evidence of a linear association and kept the age range of our categories relatively small. Although only marginally significant, we also found that the oldest (>80 years) patients tended to wait less for their diagnoses, which was consistent with the findings of Gorin et al. (13).

A history of benign breast disease and an early stage (Stage 0-II) were also independently associated with a longer diagnostic process. The benign breast disease association was marginally

significant and might be explained by two factors 1) past positive screenings with negative diagnosis leading to comfort with and acceptance of, a less timely work up 2) difficulty in reaching a benign diagnosis due to multiple lesions (including possible past biopsy scars) in dense breasts. Further study of this question is warranted. An early stage was associated with an extra 9 days to make the diagnosis. The literature has repeatedly seen that early-staged patients take longer to be diagnosed (33). This is likely explained by a lower sense of urgency associated with early-stage cancers and thus doctors were less likely to act rapidly in the diagnostic work-up.

In the literature, the clinical benefits associated with a shorter abnormal screening resolution are inconclusive and we found no guidance about a clinically acceptable diagnostic interval (143;242). The current 7-week target is based on a review of existing guidelines, tumor progression and patient quality of care research (23;145). Some investigators have demonstrated that abnormal screening follow-up taking 6 or more months is associated with a larger tumor and more positive lymph nodes (9;35;126). Conversely, others have found that patients who waited more than 2 months had smaller tumors (243) and we made a similar, albeit more modest, observation in that the Stage 0-I patients waited 9 days longer. This phenomenon was explained by Olivotto and colleagues as "the tendency of physicians to facilitate the diagnostic process for women with more suspicious abnormalities" (126), which is alternatively known as "confounding by indication" (124).

Shortening the time to diagnosis can improve the patient experience, as women often suffer from stress, anxiety and daily disruptions waiting for a diagnosis (28;104;126;131;244) and there is considerable evidence suggesting that a rapid diagnosis leads to a reduced level of anxiety among patients with benign lesions (134;140;143;244). The psychological effect of diagnostic timeliness particularly for breast cancer patients is less studied in the literature. In one study, breast cancer patients with a navigator had a significantly shorter diagnostic interval and a lower level of anxiety (245), indicating possible psychological benefits of a timely diagnosis.

Regardless of the level of scientific evidence, the psychological tensions associated with diagnostic waiting times are substantial and incontrovertible, and descriptive evidence suggests that a quicker diagnosis can considerably ease the psychological anxiety and distress (22;246). Therefore, a 9-day decrease in the diagnostic interval along with the emotional and social support provided at a DAU may have significant psychological implications for breast cancer patients.

This study has several limitations. First, we had to assume that a screening mammogram within 6 months prior to diagnosis performed outside the OBSP was abnormal as we did not have information on those tests results. Some of the OHIP screening mammograms might have had negative results while less than five percent of patients might have had an abnormal screening test earlier than 6 months before diagnosis. This could have biased our results in either direction, but the magnitude of this influence was expected to be small (see Appendix B). Second, the OHIP codes specifying the purpose of a mammogram (screening vs. diagnostic) were introduced in Oct 1st, 2010 and might not be widely adopted in clinical practice during the study period. This could have resulted in the exclusion of some OHIP screen-detected patients whose screening mammogram was miscoded as diagnostic. This might cause potential bias in the study results because the exclusion only applies to patients with the OHIP screening mammograms who were more likely to be diagnosed in UC. We think the magnitude of this influence is likely to be small as frequency of use of the new code increased from October through December 2010 and had leveled off by 2011 (247). Third, the determination of DAU use was subject to misclassification (see Appendix C). This misclassification only applies to the smaller (22.7%) group of patients detected through opportunistic screening, and would have resulted in an underestimate of the difference in time to diagnosis between DAU and UC. The facilities assigned to the UC route varied in the amount of diagnostic coordination they conducted and some of these facilities have formal partial diagnostic assessment services. This variation would have decreased the magnitude of DAU's effect that we were able to observe. Fourth, we were not able to measure some

potential confounders and we had limited quality of the measurement of covariates using administrative databases. For example, we were not able to measure confounding by indication, which indicates the phenomenon that doctors expedite the diagnostic process for patients with a higher level of cancer suspicion. Our inclusion of stage in the multivariate model partially addressed this issue. Unmeasured confounding and residual confounding effects might have influenced the study results. Fifth, our study results were restricted to the subset of breast cancer patients and might not be generalizable to patients with benign breast abnormalities. We expect a longer diagnostic interval for patients with benign breast disease as evidence suggests that women with invasive breast cancer get a quicker diagnosis compared to those with benign diseases (45;164). We were not able to assess DAUs' impact on the timeliness of diagnosis for patients with benign breast diseases. Lastly, we were only able to examine one potential outcome of DAU, a more comprehensive evaluation of DAUs' impact on patient satisfaction, quality of care, long-term survival benefits and cost-effectiveness is needed.

5.6 Conclusion

This is the first study providing information on the length of the diagnostic interval and use of DAUs among breast cancer patients detected by screening in Ontario. We found a median diagnostic follow-up of 29 days and use of DAU was expected to be determined geographically. This is also the first study examining the population-level effect of Ontario DAUs on the timeliness of diagnostic resolution in breast cancer patients. Our study demonstrated that the average diagnostic follow-up for women at DAUs was 8.3 days shorter than that of patients in usual care. This study provides an evidence base for future research examining clinical, psychological and cost-effectiveness implications associated with DAU. Further documentation as to how DAUs were able to achieve a more timely diagnosis is warranted. Future studies examining the most effective component of DAU in reducing the time to diagnosis and associated cost/resources allocations will inform breast cancer program planning.

5.7 Acknowledgements

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Table 5-1: Characteristics of breast cancer patients whose disease was detected by screening in Ontario, 2011 (N=2499)

	Total *N (%)*	*UC* *N (%)*	*DAU* *N (%)*	*P-value*
Age				
<50	158(6.3)	79(6.5)	79(6.2)	0.08
50-59	783(31.3)	406(33.4)	377(29.4)	
60-69	953(38.2)	448(36.9)	505(39.3)	
70-79	498(19.9)	224(18.4)	274(21.3)	
80+	107(4.3)	58(4.8)	49(3.8)	
Deprivation index quintile				
1 (lowest)	656(29.8)	321(29.6)	335(29.9)	0.52
2	516(23.4)	266(24.6)	250(22.3)	
3	444(20.2)	204(18.8)	240(21.5)	
4	347(15.8)	175(16.2)	172(15.4)	
5 (highest)	239(10.9)	117(10.8)	122(10.9)	
Missing	297	132	165	
Benign breast disease history				
Yes	271(10.8)	140 (11.5)	131(10.2)	0.29
No	2228(89.2)	1075(88.5)	1153(89.8)	
Recent immigrant				
Yes	96(3.8)	48(3.9)	48(3.7)	0.78
No	2403(96.2)	1167(96.1)	1236(96.3)	
Co-morbidity*				
0-3 ADGs	547(21.9)	253(20.8)	294(22.9)	0.14
4-5 ADGs	544(21.8)	258(21.2)	286(22.3)	
6-7 ADGs	495(19.8)	261(21.5)	234(18.2)	
8-9 ADGs	439(17.6)	202(16.6)	237(18.5)	
10+ ADGs	474(19.0)	241(19.8)	233(18.2)	
Urban/Rural residence				
Rural	250(10.0)	100(8.2)	150(11.7)	0.004
Urban	2247(90.0)	1114(91.8)	1133(88.3)	

* Co-morbidity was evaluated using the Johns Hopkins Aggregated Diagnosis Groups (ADGs). Each ADG represents one cluster of disease with similar clinical criteria and expected needs for health care.

Table 5-2: Disease characteristics of breast cancer patients whose disease was detected by screening in Ontario, 2011 (N=2499)

	Total ***N (%)***	***UC*** ***N (%)***	***DAU*** ***N (%)***	***P-value***
Histological grade				
Low	685(29.9)	319 (28.9)	366 (30.8)	0.36
Medium	1086(47.4)	540 (48.9)	546 (46.0)	
High	521(22.7)	245 (22.2)	276 (23.2)	
Missing	207	111	96	
Tumor size				
<=15mm	1278(51.1)	615(50.6)	663(51.6)	0.51
16-35mm	960(38.4)	471(38.8)	489(38.1)	
16-55mm	138(5.5)	66(5.4)	72(5.6)	
56-300mm	77(3.1)	35(2.9)	42(3.3)	
Diffuse/non-palpable/UNK/missing	46(1.8)	28(2.3)	18(1.4)	
Stage				
Stage 0-I	1520(61.8)	729 (61.0)	791(62.5)	0.03
Stage II	727(29.5)	344 (28.8)	383(30.3)	
Stage III-IV	214(8.7)	122 (10.2)	92(7.3)	
Stage UNK/missing	38	20	18	

Table 5-3: Usual health care utilization characteristics of breast cancer patients whose disease was detected by screening in Ontario, 2011 (N=2499)

	Total *N (%)*	*UC* *N (%)*	*DAU* *N (%)*	*P-value*
Frequency of doctor visits				
<10	980(39.2)	448(36.9)	532(41.4)	0.12
10-19	838(33.5)	419(34.5)	419(32.6)	
20-29	391(15.7)	197(16.2)	194(15.1)	
30+	290(11.6)	151(12.4)	139(10.8)	
Primary care provider				
Yes	2370(94.8)	1165(95.9)	1205(93.9)	0.02
No	129(5.2)	50(4.1)	79(6.1)	
Preventive services index*				
Median(IQR)	0.40(0.2-0.7)	0.40(0.2-0.7)	0.40(0.2-0.7)	0.06
Continuity of care				
Non-users	617(8.9)	78(6.4)	100(7.8)	0.22
Low	1951(28.3)	304(25.0)	341(26.6)	
High	4330(62.8)	833(68.6)	843(65.6)	

* Preventive service index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible

Table 5-4: Diagnostic interval (days) for breast cancer patients whose disease was detected by screening in Ontario, 2011

	N (%)	*Median*	*25th Percentile*	*75th Percentile*	*90th Percentile*	*% Resolved within 7 weeks*
Total	2499 (100)	29	17	50	79	74.8
UC	1215 (48.6)	35	20	55	82	70.2
DAU	1284 (51.4)	26	15	43	77	79.1

Table 5-5: Bivariate and multivariate analyses of factors associated with diagnostic interval between the abnormal screening test and diagnosis for women with screen-detected breast cancer in Ontario, 2011 (N=2499)

	Crude Difference (days) in Median Diagnostic Interval (95% CI)	Adjusted Difference (days) in Median Diagnostic Interval[†] (95% CI)
Diagnostic route		
DAU	-9(-11.6, -6.4)	-8.3(-10.2, -6.5)
Usual Care	Ref	Ref
Age		
<50	-1(-5.1, 3.1)	-1.0(-5.3, 3.3)
50-59	0(-2.1, 2.2)	-0.4(-2.9, 2.2)
60-69	Ref	Ref
70-79	4(0.9, 7.1)	4.0(1.3, 6.7)
80+	-4(-10.0, 2.0)	-3.8(-8.0, 0.5)
Deprivation index quintile		
1 (lowest)	Ref	Ref
2	0(-2.9, 2.9)	-1.3(-4.2, 1.5)
3	2(-1.5, 5.5)	2.1(-1.3, 5.6)
4	1(-2.4, 4.4)	-0.6(-4.0, 2.7)
5 (highest)	0(-4.4, 4.4)	0.2(-3.5, 4.0)
Missing	-1(-4.9, 3.0)	-1.3(-5.0, 2.4)
Benign breast disease history		
Yes	2(-1.6, 5.6)	3.0(-0.1, 6.1)
No	Ref	Ref
Recent Immigrant		
Yes	4(-1.0, 9.0)	3.9(-1.0, 8.8)
No	Ref	Ref
Co-morbidity[*]		
0-3 ADGs	Ref	Ref
4-5 ADGs	0(-2.9, 2.9)	-0.5(-3.5, 2.5)
6-7 ADGs	0(-3.2, 3.2)	1.6(-2.4, 5.5)
8-9 ADGs	1(-2.7, 4.7)	2.3(-1.6, 6.3)
10+ ADGs	2(-1.5, 5.5)	0.2(-4.2, 4.5)
Urban/Rural residence		
Urban	Ref	Ref
Rural	1(-3.5, 5.5)	1.4(-2.6, 5.4)
Histological grade		
Low	2(-1.7, 55.7)	1.0(-1.8, 3.8)
Medium	1(-1.8, 3.8)	0.9(-1.5, 3.2)
High	Ref	Ref
Missing	8(1.2, 14.2)	9.3(4.2, 14.4)
Stage		
Stage 0-I	9(4.0, 14.0)	9.9(6.5, 13.4)
Stage II	2(-3.1, 7.1)	3.7(0.1, 7.3)

Stage III-IV	Ref	Ref
Stage UNK/missing	-1(-12.1, 10.1)	-9.5(-19.0, -0.1)
Frequency of doctor visits		
<10	-1(-3.0, 1.0)	0.5 (-2.5, 3.4)
10-19	Ref	Ref
20-29	3(-0.7, 6.7)	2.1(-1.6, 5.8)
30+	1(-2.6, 4.6)	-0.6 (-4.9, 3.7)
Preventive services index[**]		
Parameter Estimate	0.8 (-1.3, 3.0)	0.4(-3.0, 3.8)
Primary care provider		
Yes	Ref	Ref
No	0(-3.9, 3.9)	1.8(-2.9, 6.5)
Continuity of care		
Non-users	0(-3.5, 3.5)	0.6(-3.9, 5.1)
Low	1(-2.2, 4.2)	0.9(-1.6, 3.4)
High	Ref	Ref

[†] adjusted for all study covariates.

[*] Co-morbidity was evaluated using the Johns Hopkins Aggregated Diagnosis Groups (ADGs). Each ADG represents one cluster of disease with similar clinical criteria and expected needs for health care.

[**] Preventive service index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible

Chapter 6

A Population-Based Study of the Effect of a Specialized Diagnostic Unit on the Diagnostic Interval in Symptomatic Breast Cancer Patients

6.1 Abstract

Background: The diagnostic assessment unit (DAU) is an organizational structure designed to provide a seamless transition from abnormality detection to definitive diagnosis. Ontario DAUs are comprised of Breast Assessment Affiliates (BAA) and regional breast assessment centres. This study examined the length of the diagnostic interval for symptomatic breast cancer patients diagnosed through a DAU versus those diagnosed through usual care.

Methods: This was a retrospective population-based cohort study of 4381 symptomatic patients with invasive breast cancer diagnosed between Jan 1st, 2011 and December 31st, 2011. Study data sources included administrative databases available at the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario (CCO). The diagnostic interval was defined as the time from patients' index contact to the cancer diagnosis. DAU use was assigned based on the hospital where a breast biopsy/surgery was performed. Multivariate median regression was used to study the DAU effect on the diagnostic interval while adjusting for possible confounders.

Results: Overall, the median time to diagnosis was 34 days. Forty-seven percent of patients were diagnosed in a DAU and fifty-three percent of patients were diagnosed in UC. DAUs had a higher rate in achieving the Canadian timeliness targets compared to UC (71.7% vs. 58.1%). DAU use was associated with a 12-day reduction in the diagnostic interval (95% CI: 9.5-14.5) compared to usual care. The adjusted DAU effect was 10 days (95% CI: 7.8-11.9).

Conclusions: Results of this study demonstrated that Ontario DAUs were significantly associated with a shorter diagnostic interval for symptomatic breast cancer patients. A 10-day decrease in time to diagnosis might have a substantial influence on the patient experience including the reduction of psychological tensions evoked by diagnostic waiting times. Future research examining DAU's effect on a more comprehensive range of quality of care indicators is warranted.

6.2 Introduction

Breast cancer is the most common cancer among Ontario women with estimates of 9100 incident cases and 2000 deaths in 2012 (18;19). The majority of (more than 50%) of breast cancer patients first presented with signs/symptoms (28;94;233) and many of them waited weeks to get a cancer diagnosis (6;243). Waiting for a diagnosis constitutes an extremely stressful period for women and their families, often with experiences of distress, anxiety and fear about breast cancer (20-22). Besides, a delay between 3 and 6 months in diagnosis has been associated with an advanced cancer stage and poorer survival (23). The Public Health Agency of Canada has set Canadian timeliness targets for abnormal screening follow-up, recommending that 90% of patients should have abnormal screening results resolved within 5 weeks (if no tissue biopsy is required) or within 7 weeks (if a tissue biopsy is required) (145;146).

In 2004, Cancer Care Ontario introduced the diagnostic assessment unit (DAU) which is designed to improve the patient experience and quality of care through a seamless transition from abnormality detection to definitive diagnosis (25). Ontario DAUs are comprised of the organized breast assessment affiliates (BAA) that are under the auspices of the Ontario Breast Screening Program (OBSP), and breast assessment centres that are independently developed across Ontario. DAUs have been structured to provide centralized and coordinated diagnostic services by a multidisciplinary team that includes a nurse navigator. To the best of our knowledge, the population-level influence of Ontario DAUs on the timeliness of diagnosis for symptomatic breast cancer patients has not been assessed. The purpose of this study, therefore, was to examine the association between DAU use and the length of the diagnostic interval for symptomatic breast cancer patients in Ontario.

A conceptual framework adapted from the Chronic Care Model (152) was used to understand diagnostic care and guide the study design. As Figure 6-1 demonstrated, the diagnostic process starts from patients' index contact with the health care system and ends at the

definitive diagnosis. This framework is centred on the ideal situation whereby productive encounters occur between active patients and prepared provider teams within the context of an optimal health system, with those productive encounters ultimately leading to an optimal diagnostic interval. We conceptualized the DAU as a system-level factor encompassing many of the support structures presented in our framework. We evaluated DAU use and its association with the length of the diagnostic interval while controlling for other non-system factors. The factors we examined and controlled for were: patient characteristics (age, recent immigration status, urban/rural residence, socio-economic status, co-morbidity, and benign breast disease history), disease characteristics (tumor size, stage and histological grade), physician characteristics (age, sex, years in practice, clinical volume, and clinical practice settings) and usual health utilization characteristics (frequency of doctor visits, access to a primary care provider, continuity of care and use of preventive services).

6.3 Study Design and Data Sources

We conducted a population-based retrospective cohort study of symptomatic breast cancer patients diagnosed between Jan 1st, 2011 and Dec 31st, 2011 in Ontario, Canada. We used the Ontario Cancer Registry to identify all incident breast cancer cases and their dates of diagnosis. Breast-related services and associated dates and physicians, diagnostic codes, diagnostic institutions, past disease histories, and the usual health care utilization were identified from four administrative databases from the Canadian province of Ontario, including the Ontario Health Insurance Plan Claims Database (OHIP), the Canadian Institute for Health Information/ Discharge Abstract Database (CIHI/DAD), the National Ambulatory Care Reporting System (NACRS), and the Same-day Surgery Database (SDS). The Ontario Breast Screening Program Database contains information on screening mammograms and their results, and it was used in combination with the OHIP, CIHI/DAD, NACRS and SDS databases to ascertain the cancer presentation (screening vs. symptomatic). Patients' demographics were obtained from the

Registered Persons Database and physician's characteristics were obtained from the Institute for Clinical Evaluative Sciences (ICES) Physician Database combined with the Client Agency Program Enrollment Data. The Collaborative Stage Data (181-184) was used to determine cancer staging (including tumor size) and the histological grade of cancer. A list of BAA hospitals was provided to us by the OBSP and a separate list of regional breast assessment centres was obtained through a survey to Cancer Care Ontario Regional Primary Care Leads and the OBSP Regional Program Managers.

6.4 Study Population

We identified all incident breast cancer patients who had 1) female sex 2) a single primary breast cancer 3) a histologically confirmed invasive cancer diagnosed between Jan 1st, 2011 and Dec 31st, 2011. We excluded patients 1) whose cancer was diagnosed at the death certificate only 2) who were living outside of Ontario at the time of diagnosis or 3) who did not have the Ontario Health Insurance Plan (OHIP) coverage for at least three years prior to the diagnosis. We excluded screen-detected breast cancer patients who are the subject of a separate study of DAU use and the diagnostic interval. We also excluded patients who initially presented through the emergency. This study was approved by the Health Sciences Research Ethics Board at Queen's University at Kingston, Canada (see Appendix E).

6.5 Outcome Definition

We developed a conservative strategy to identify the index contact that initiated the diagnostic interval based on previous studies (114;189;248). As illustrated in Figure 6-2, we looked backwards 6 months from the date of diagnosis to identify all breast-related diagnostic procedures, including diagnostic mammogram, breast ultrasound, breast magnetic resonance imaging (MRI), breast biopsy or breast surgical consultation. We picked up the earliest diagnostic test for each assessment modality and identified the most recent visit to the referring physician who ordered that test. The earliest diagnostic test or referring doctor visit was identified as the

index contact. The length of the diagnostic interval was subsequently calculated as the time between the index contact and the definitive diagnosis. We also dichotomized the diagnostic interval at 7 weeks based on the Canadian timeliness guideline which recommends that 90% of abnormal screening tests should be resolved within 7 weeks if a tissue biopsy is required (145).

6.6 DAU Use Determination

We determined if a patient was diagnosed through DAU or usual care (UC) based on the institution where the diagnostic biopsy or therapeutic surgery closest to the date of diagnosis was performed using the OHIP, NACRS, SDS and CIHI/DAD data. We validated this strategy in a separate study using a group of screen-detected breast cancer patients whose DAU use was tracked by the organized screening program for payment purposes (see Appendix C).

6.7 Covariates

Factors that were significantly associated with the length of the diagnostic interval in the literature or were possibly related to diagnostic care were selected as study covariates. We organized these variables based on the conceptual framework into four categories 1) patient characteristics 2) referring physician's characteristics 3) cancer characteristics 4) usual health care utilization characteristics.

Patient characteristics were described using age, recent immigration status, socio-economic status based on the area-level material deprivation index (195;196), benign breast disease history, urban/rural residence based on the Rurality Index for Ontario 2008 (RIO2008) scores (198) and co-morbidity based on the Johns Hopkins Aggregated Diagnosis Groups (ADGs) (201). Referring physicians' characteristics include age, sex, years in practice, clinical volume and the practice setting. Many cancer characteristics were unknown at the time of index contact and may change over time. We controlled for the relatively static aspects of disease (histological grade and cancer stage group) and described the distribution of one non-static factor (tumor size) in detail contrasting patients in the DAU and UC groups. The usual health care utilization was

assessed between 36 months and 12 months before diagnosis, as evidence suggests that a two-year look back period provides stable estimates of usual health care utilization (166). Health care utilization variables include: the number of doctor visits, having a primary care provider, the continuity of care based on the Usual Provider Continuity (UPC) index (223), and the use of preventive services. The preventive services index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible (166). Five component preventive services involved in the calculation were annual health examination, influenza vaccination, breast cancer screening, colorectal cancer screening, and cervical cancer screening.

6.8 Statistical Analysis

Both descriptive and analytical analyses were performed at ICES Queen's Health Services Research Facility using SAS statistical Program (Version 9.3, SAS Institute Inc., Cary, North Carolina). We described and compared covariates between DAU and UC to understand the variation in DAU use. We assessed bivariate associations between covariates and DAU use with two-independent-sample t-test, Wilcoxon-rank-sum test and chi-square test of independence. We also examined bivariate associations between study variables and diagnostic interval through the use of median regressions (228). A multivariate median regression model was constructed to determine the adjusted association between DAU use and breast cancer diagnostic interval. Logistic regressions were used to assess the success of DAUs in meeting recommended timeliness targets.

6.9 Results

We identified 8720 female, single primary breast cancer patients in the OCR, 2552 of which were in our screen-detected study. A further 647 patients who were living outside of Ontario at the time of diagnosis were excluded. Zero patients were diagnosed at the death certificate only, 169 patients were excluded because they did not have OHIP coverage for at least

three years prior to diagnosis and 18 patients were excluded because they presented through an Emergency Department. Due to missing institution codes on biopsy and/or surgery records we were not able to assign DAU use (yes/no) to 608 patients. The final study cohort was comprised of a total of 4381 symptomatic breast cancer patients.

Table 6-1 summarizes the characteristics of the study population by DAU use. Overall, the mean age at diagnosis was 60.4 years and 29.0% of patients were diagnosed under age 50. Patients diagnosed through a DAU had fewer co-morbidities (21.5% vs. 26.9%, p=0.001). Other patient characteristics were not significantly different between the DAU and UC groups.

Cancer characteristics, usual health care utilization characteristics and referring physicians' characteristics by DAU use are presented in Table 6-2 to Table 6-4. Patients at DAUs were less likely to have smaller tumor sizes (26.7% vs. 30.9%, p=0.002) and were less likely to have earlier stage (stage 0-I) cancers (35.1% vs. 39.1%) compared to those in UC. During a two-year usual health care utilization period, patients diagnosed through a DAU had fewer health care encounters (11 vs. 13, p<0.001), were less likely to receive an annual physical exam (28.4% vs. 32.2%, p=0.005) and were more likely to receive breast cancer screening (34.3% vs. 25.9%, p<0.001) compared to those in UC. The referring physicians associated with patients at DAUs were slightly younger, less experienced, less busy, and were more likely to be females than those associated with UC.

We compared the characteristics of 608 patients whose DAU use was unavailable with the rest of symptomatic breast cancer patients. Those excluded patients were more likely to live in the urban area (94.2% vs. 91.6%, p=0.003) and were more likely to have Stage III-IV cancer (31.2% vs. 21.0%, p<0.001).

Table 6-5 displays the diagnostic timeliness of patients. The average time to diagnosis was 34 days, with an interquartile range of 17 to 67 days. Notably, over 25% of patients waited more than 9 weeks and 10% of patients waited more than 17 weeks to reach a cancer diagnosis.

Overall, 64.5% of patients met the 7-week target, with the DAU group more likely to achieve that target than UC (OR=1.83, 95% CI: 1.6-2.1). This odds ratio did not change when controlling for possible confounders in a logistic regression analysis (OR=1.82, 95% CI: 1.6-2.1).

Results of bivariate and multivariate analyses are shown in Table 6-6. The median diagnostic interval was 12 days (95% CI: 9.5-14.5, $p<0.001$) shorter for patients diagnosed through DAUs than UC. In a multivariate median regression model, DAU significantly shortened the time to diagnosis by 9.9 days (95% CI: 7.8-11.9, $p<0.001$) compared to UC after adjusting for all covariates. Age below 50 or above 69 (vs. age 60-69) was a significant predictor for a shorter diagnostic interval ($p<0.05$ for all categories). A benign breast disease history ($p<0.001$), a well/moderately differentiated tumor ($p<0.001$) and an early stage cancer (Stage 0-II) ($p<0.001$) were significantly associated with a prolonged diagnostic interval. A referring physician who practiced less than 20 years (vs. 30-40 years) was associated with a 7-day delay in the diagnostic process ($p=0.01$).

6.10 Discussion

This study provides the first empirical evidence to understand the population-level effect of Ontario DAUs on the time to diagnosis for symptomatic breast cancer patients. DAUs significantly shortened the time to diagnosis by 30% (28 days vs. 40 days) compared to the usual care route (UC). After controlling for potential confounders, this effect estimate declined by 21% to 9.9 days, which is comparable to an 8-day reduction associated with a "fast-track referral" reported by Borugian et al (164) and a 6-day time reduction attributed to a patient navigator program in Nova Scotia (163). Ontario DAUs seem to result in a more timely diagnosis than those two programs, which is likely explained by the fact that both the patient navigation and "fast-track referral" were included in the DAU's organizational design.

DAUs had a higher rate in achieving Canadian timeliness targets than UC (71.7% vs. 58.1%). Symptomatic patients diagnosed within the targeted 7 weeks were significantly more

likely to use DAUs than UC after adjusting for possible confounders (OR=1.82, 95% CI: 1.6-2.1). Compared to previous evidence from the OBSP (28), we observed a higher proportion of patients diagnosed within targeted time frame in both the DAU and UC groups. This might be due to the different study populations, as symptomatic breast cancer patients are likely to have a more obvious clinical presentation or provoke more sense of urgency than those with abnormal screening results, resulting in a faster diagnosis.

Ontario DAU's achievement may be attributed to its structural design (24-27;149). Ontario DAUs employs a patient navigator to organize diagnostic services and guide patient through the health care system. Diagnostic investigations are centrally arranged by a patient navigator in a DAU without re-referral from the primary care provider. Ontario DAUs also provide breast diagnostic services in a multidisciplinary environment and ensure good availability of diagnostic equipment and clinical expertise. The mechanisms through which the DAUs expedite the diagnostic process need to be further examined.

The structure of DAUs in other jurisdiction varies. The United Kingdom and some European countries have initiated special symptomatic breast cancer clinics that adopted a "triple assessment" approach, which performs clinical examinations, diagnostic imaging tests (mammography, breast ultrasound) and fine needle aspiration cytology during one clinic visit (249). Evidence shows that these DAUs are successful in facilitating the diagnostic process (250;251). The international development of DAUs reflects a trend that system-level reorganizations are necessary to achieve a timely diagnosis.

An important question, however, is how a shortened diagnostic interval is related to clinical outcomes. The literature contains conflicting evidence. Some studies reported no association between the time to diagnosis and the cancer prognosis (117), while others found that a shorter diagnostic interval significantly predicted a poorer prognosis (243). This latter phenomenon is most likely due to confounding by indication, which means that patients with

symptoms highly indicative of cancer receive more medical attention from physicians and thus have a quicker diagnosis (124;252). Although a 10-day reduction in diagnostic work-up may not affect clinical outcomes, it may reduce patients' anxiety and distress associated with diagnostic wait times (104;130-132).

Approximately half (46.7%) of all symptomatic breast cancer patients were diagnosed at Ontario DAUs during 2011, which was higher than a reported rate of 39% in 2007 among all Ontario women with abnormal OBSP screening (28). The increased number of DAUs from 25 in 2007 to 47 in 2011 likely explains this discrepancy. Openings during and since our study period have likely increased this rate. Seven of eighteen patient demographics, disease characteristics, referring physician's characteristics and patient usual health utilization factors slightly differed between the DAU and UC groups, with an absolute difference ranging from 3.3% to 5.4%. Overall, we think that being diagnosed at a DAU versus UC was largely determined by where a woman lived but some selection bias may also be present in the data so we cannot rule out lack of control of unmeasured confounders.

This study also provides information on the length of the diagnostic interval for symptomatic breast cancer patients at a provincial level. A median diagnostic interval of 34 days in Ontario was comparable to 35 days reported in Quebec (11), but it was longer than the median of 18 days reported in the United States (5) and 15 days reported in Germany (6). Different health care settings/policies such as the guideline of "two-week" referral in the United Kingdom might explain the inconsistency (144). Of our particular concern is the finding that approximately 25% of symptomatic breast cancer patients waited more than 9 weeks to establish a cancer diagnosis and 10% had a diagnostic interval greater than 17 weeks are worrisome, as such amount of delay can lead to a poorer survival based on the established evidence (23). These 75^{th} and 90^{th} percentiles were also longer than those reported from organized breast screening programs (104), indicating that symptomatic breast cancer patients are more vulnerable to a delayed diagnosis.

Age below 50 and age above 69 (vs. 60-69) were significantly associated with a 4-day decrease in the diagnosed interval, independent of all variables controlled in the multivariate model. This contradicts with most previous findings that a younger age was associated with a prolonged diagnostic interval (13;14). The discrepancy may be explained by differences in study methodologies where some categorized the diagnostic interval for analyses (14) while some did not use multivariate analyses (44;158). We analyzed the length of the diagnostic interval as continuous using multivariate regression to control for possible confounders. Younger patients are likely to feel urgent about the breast abnormality and thus might actively seek for a faster diagnosis. Also, younger women with pre-menopausal breast cancers are likely to have a more aggressive clinical appearance which generates more attentions from doctors (253). Women aged above 80 might have very unique characteristics such as being more health-conscious or having less dense breast tissues that possibly reduce the time to diagnosis. Elderly patients (aged above 80) are also likely to have bigger tumor size that generates higher cancer suspicion (254).

A history of benign breast diseases, a lower-grade tumor and an early-stage cancer were significant predictors of a longer diagnostic interval, which are consistent with the literature (16;33). The delay in diagnosis associated with the presence of benign breast disease might be explained by a lower suspicion of malignancy due to the past false positive results or the increased difficulty in reaching a diagnosis due to past multiple lesions or biopsy scars. The delay in diagnosis associated with well-differentiated cancers might be explained by a less aggressive appearance of disease that did not generate medical attentions for a rapid diagnosis. Well-differentiated tumors usually have common symptoms with benign breast diseases, increasing the difficulty of reaching a diagnosis (255). Similarly, early-stage cancers were likely not treated with sense of urgency and thus lead to a prolonged diagnostic interval (33).

This study has a number of strengths. First, the use of administrative database enabled us to study the entire symptomatic breast cancer population in Ontario. Also, we were able to detect

small differences with a large sample size. Second, the study filled in the knowledge gap in understanding the length of the diagnostic interval and DAU use in symptomatic breast cancer patients at a provincial level. Third, this study provided the first empirical evidence on the population-level effects of DAU on the timeliness of diagnosis in symptomatic breast cancer patients. Fourth, a conceptual framework was used to understand factors associated with the diagnostic interval and guide the study design. We controlled for a large number of risk factors when assessing the association between DAU use and the diagnostic interval. Fifth, the median regression modeling provides estimates that were statistically robust and easy to interpret for knowledge transfer purposes.

This study also had some limitations. First, some screen-detected patients might have been misclassified as symptomatic and included in this study as a result of two factors: 1) an OHIP screening mammogram within 6 months prior to diagnosis was assumed abnormal as administrative databases did not contain test results; 2) the Ontario Health Insurance Plan (OHIP) codes that enabled us to differentiate between the purposes of mammogram (screening vs. diagnostic) were introduced in late 2010, and some screening mammograms might have been miscoded as diagnostic. Both situations might have biased DAU's effect but with unpredictable direction, as the literature contains conflicting evidence on the association between the cancer presentation (screen-detected vs. symptomatic) and the diagnostic interval (11;13;14;29;31). However, we expected the amount of influence to be small in that less than 5% of the OBSP screen-detected patient waited more than 6 months for a diagnosis (see Appendix B) and we saw an abrupt jump in the claims of new OHIP fee codes in 2011 (256). Second, we identified the index contact based on the most recent (referring) doctor visit before the first breast-specific diagnostic test, which was conservative and likely have underestimated the length of the diagnostic interval. Third, there might also have been misclassifications on DAU use (see Appendix C). We determined DAU use based on the hospital where a biopsy/surgery that was

performed closest to the date of diagnosis, as use of DAUs was not tracked for symptomatic patients. Misclassifications were similar between UC and DAU, with slightly more (6%) UC patients misclassified as DAU patients. This might have underestimated DAUs' effect by driving the median diagnostic interval in the DAU group towards UC. In addition, the facilities assigned to the UC route varied in the amount of diagnostic coordination they conducted and some of these facilities have formal partial diagnostic assessment services. This variation would have decreased the magnitude of DAU's effect on timeliness of diagnosis that we were able to observe. Fourth, we excluded 608 (12.2%) breast cancer patients whose DAU use was unavailable. Compared to the rest of the symptomatic patients, they were more likely to live in an urban area and were more likely to have advanced-stage cancer. Exclusion of this group might have overestimated the length of the diagnostic interval and introduced bias to DAUs' effect. Fifth, the study results were restricted to a cohort of breast cancer patients. Evidence suggests that women with invasive breast cancer get a quicker diagnosis compared to those with benign diseases (45;164). So we expected a longer diagnostic interval for patients without breast cancer. We were not able to assess DAUs' effect among the patients who had benign breast abnormalities. Lastly, study results are subject to unmeasured confounding and residual confounding effects. We identified a list of potential confounders that were associated with diagnostic interval by reviewing the literature, but we were only able to measure a subset of these variables since we were restricted to using administrative databases. Factors might have confounded the association between DAU use and breast cancer diagnostic interval if they were unevenly distributed between the DAU and UC groups. Additionally, administrative databases may not provide accurate measurement of study covariates due to the limited data quality. Residual confounding effects might have affected the study results.

6.11 Conclusion

This study demonstrated that use of a DAU was associated with a shorter diagnostic interval for symptomatic Ontario breast cancer patients. This effect may be explained by DAU's

unique organizational components. Future research investigating the mechanism of DAU in achieving a more timely diagnosis is warranted. Also, a more comprehensive evaluation is needed to understand DAU's influence on clinical outcomes, psychological outcomes, patient satisfaction, quality of care, and system cost-effectiveness.

6.12 Acknowledgements

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Table 6-1: Characteristics of symptomatic breast cancer patients in Ontario, 2011 (N=4381)

	Total ***N (%)***	**UC** ***N (%)***	**DAU** ***N (%)***	**P-value**
Age				
<50	1269(29.0)	647(27.7)	622(30.4)	0.13
50-59	958(21.9)	540(23.1)	418(20.4)	
60-69	883(20.2)	468(20.0)	415(20.3)	
70-79	654(14.9)	343(14.7)	311(15.2)	
80+	617(14.1)	338(14.5)	279(13.6)	
Deprivation index quintile				
1 (lowest)	1135(29.2)	577(27.6)	558(31.0)	0.17
2	857(22.1)	466(22.3)	391(21.7)	
3	738(19.0)	412(19.7)	326(18.1)	
4	629(16.2)	337(16.1)	292(16.2)	
5 (highest)	528(13.6)	296(14.2)	232(12.9)	
missing	494	248	246	
Benign breast disease history				
Yes	647(14.8)	359(15.4)	288(14.1)	0.23
No	3734(85.2)	1977(84.6)	1757(85.9)	
Recent immigrant				
Yes	277(6.3)	155(6.6)	122(6.0)	0.36
No	4104(93.7)	2181(93.4)	1923(94.0)	
Co-morbidity*				
0-3 ADGs	1051(24.0)	502 (21.5)	549 (26.9)	0.001
4-5 ADGs	884(20.2)	499 (21.4)	385 (18.8)	
6-7 ADGs	915(20.9)	499 (21.4)	416 (20.3)	
8-9 ADGs	689(15.7)	371 (15.9)	318 (15.6)	
10+ ADGs	842(19.2)	465 (19.9)	377 (18.4)	
Urban/Rural residence				
Rural	368(8.4)	188(8.1)	180(8.8)	0.37
Urban	4011(91.6)	2147(91.9)	1864(91.2)	

* Co-morbidity was evaluated using the Johns Hopkins Aggregated Diagnosis Groups (ADGs). Each ADG represents one cluster of disease with similar clinical criteria and expected needs for health care.

Table 6-2: Disease characteristics of symptomatic breast cancer patients in Ontario, 2011 (N=4381)

	Total ***N (%)***	**UC** ***N (%)***	**DAU** ***N (%)***	**P-value**
Histological grade				
Low	738(19.7)	393(20.0)	345(19.3)	0.84
Medium	1679(44.8)	879(44.8)	800(44.8)	
High	1330(35.5)	690(35.2)	640(35.9)	
Missing	634	374	260	
Tumor size				
<=15mm	1266(28.9)	721(30.9)	545(26.7)	0.002
16-35mm	2015(46.0)	1038(44.4)	977(47.8)	
16-55mm	560(12.8)	286(12.2)	274(13.4)	
56-300mm	372(8.5)	187(8.0)	185(9.1)	
Diffuse/non-palpable/UNK/missing	168(3.8)	104(4.5)	64(3.1)	
Stage				
Stage 0-I	1579(37.2)	879 (39.1)	700 (35.1)	0.03
Stage II	1778(41.9)	917 (40.8)	861 (43.1)	
Stage III-IV	890(21.0)	454 (20.2)	436 (21.8)	
Stage UNK/missing	134	86	48	

Table 6-3: Usual health care utilization characteristics of symptomatic breast cancer patients in Ontario, 2011 (N=4381)

	Total ***N (%)***	**UC** ***N (%)***	**DAU** ***N (%)***	**P-value**
Frequency of doctor visits				
Median(IQR)	12(6-21)	13(6-22)	11(6-20)	<0.001
Preventive services index*				
Median(IQR)	0.4(0.2-0.8)	0.4(0.2-0.8)	0.4(0.1-0.7)	0.09
Continuity of care				
Non-users	430(9.8)	211(9.0)	219(10.7)	0.07
Low	1304(29.8)	681(29.2)	623(30.5)	
High	2647(60.4)	1444(61.8)	1203(58.8)	
Primary care provider				
Yes	4066(92.8)	2176(93.1)	1890(92.4)	0.35
No	315(7.2)	160(6.9)	155(7.6)	

* Preventive service index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible

Table 6-4: Referring physicians' characteristics (N=4381)

	Total ***N (%)***	**UC** ***N (%)***	**DAU** ***N (%)***	**P-value**
Years in practice				
<=20	1246	630(27.5)	616(30.8)	<0.001
21-30	1407	724(31.6)	683(34.2)	
31-40	1164	654(28.6)	510(25.5)	
41+	471	281(12.3)	190(9.5)	
Missing	93	47	46	
Clinical volume(per 1000)				
Median(IQR)	4.9(3.4-7.1)	5.1(3.4-7.3)	4.7(3.3-6.8)	<0.001
Practice setting				
Rostered practice	1053(24.0)	587(25.1)	466(22.8)	0.111
Non-rostered practice	2876(65.7)	1501(64.3)	1375(67.2)	
Other	452(10.3)	248(10.6)	204(10.0)	
Physician sex				
Female	1812(42.1)	912(39.7)	900(44.9)	<0.001
Male	2489(57.9)	1384(60.3)	1105(55.1)	
Missing	80	40	40	
Physician specialty				
FP/GP	3929(91.5)	2088(91.0)	1841(92.0)	0.427
Diagnostic Radiologists/Radiation Oncologist.	30(0.7)	17(0.7)	13(0.6)	
General Surgeon	177(4.1)	105(4.6)	72(3.6)	
Other	160(3.7)	84(3.7)	76(3.8)	
Missing	85	42	43	

Table 6-5: Diagnostic interval (days) for symptomatic breast cancer patients in Ontario, 2011

	N (%)	*Median*	*25th Percentile*	*75th Percentile*	*90th Percentile*	*Diagnosed within 7 weeks (%)*
Total	4381(100)	34	17	67	121	64.5
UC	2336(53.3)	40	21	78	135	58.1
DAU	2045(46.7)	28	15	54	106	71.7

Table 6-6: Bivariate and multivariate analyses of factors associated with diagnostic interval between the index contact and diagnosis for women with symptomatic breast cancer in Ontario, 2011 (N=4381)

	Crude Difference (days) in Median Diagnostic Interval (95% CI)	Adjusted Difference (days) in Median Diagnostic Interval (95% CI)[†]
Diagnostic route		
DAU	-12(-14.6, -9.5)	-9.9(-11.9, -7.8)
Usual Care	Ref	Ref
Age		
<50	-7(-11.0, -3.0)	-4.5(-8.0, -0.9)
50-59	-1(-5.4, 3.4)	-1.0(-4.7, 2.7)
60-69	Ref	Ref
70-79	-5(-10.0, -0.0)	-4.1(-7.6, -0.5)
80+	-9(-13.2, -4.8)	-8.8(-12.5, -5.2)
Deprivation index quintile		
1 (lowest)	Ref	Ref
2	-1(-5.0, 3.0)	-1.2(-4.0, 1.7)
3	3(-1.1, 7.1)	2.9(-0.2, 5.9)
4	2(-1.9, 5.9)	2.3(-1.2, 5.8)
5 (highest)	3(-1.2, 7.2)	2.8(-1.2, 6.8)
Missing	-3(-7.1, 1.1)	-2.9(-7.0, 1.3)
Benign breast disease history		
Yes	15(9.3, 20.7)	8.0(3.4, 12.6)
No	Ref	Ref
Recent immigrant		
Yes	3(-2.0, 8.0)	2.5(-1.7, 6.6)
No	Ref	Ref
Co-morbidity[*]		
0-3 ADGs	Ref	Ref
4-5 ADGs	4(0.2, 7.8)	1.5(-1.9, 4.9)
6-7 ADGs	7(3.4, 10.6)	1.0(-2.6, 4.7)
8-9 ADGs	6(2.6, 9.4)	0.6(-3.9, 5.0)
10+ ADGs	9(4.9, 13.1)	2.0(-2.9, 7.0)
Urban/Rural residence		
Urban	Ref	Ref
Rural	0(-4.8, 4.8)	2.4(-2.4, 7.3)
Histological grade		
Low	16(11.7, 20.3)	9.3(5.5, 13.1)
Medium	8(5.4, 10.6)	4.6(2.1, 7.1)
High	Ref	Ref
Missing	4(-0.2, 8.2)	3.6(0.2, 7.1)
Stage		
Stage 0-I	23(19.2, 26.8)	17.2(13.9, 20.4)
Stage II	6(3.3, 8.7)	4.8(2.4, 7.2)

Stage III-IV	Ref	Ref
Missing	12(3.7, 20.3)	11.5(2.6, 20.3)
Frequency of doctor visits		
Parameter estimate	0.2(0.1, 0.3)	0.1(0.0, 0.2)
Preventive services index[**]		
Parameter estimate	2.9(-0.1, 5.9)	-0.2(-2.8, 2.4)
Primary care provider		
Yes	Ref	Ref
No	-11(-14.0, -8.0)	-1.7(-5.8, 2.3)
Continuity of Care		
Non-users	-8(-11.0, -5.0)	-1.5(-5.3, 2.2)
Low	-1(-4.4, 2.4)	0.9(-1.7, 3.5)
High	Ref	Ref
Physician age		
Parameter estimate	0.1(-0.0, 0.2)	0.3(0.1, 0.6)
Years in practice		
<=20	Ref	Ref
21-30	2(-1.1, 5.1)	-2.5(-6.6, 1.6)
31-40	0(-3.3, 3.3)	-7.3(-13.1, -1.6)
41+	4(-0.6, 8.6)	-6.0(-13.9, 2.0)
Missing	-12(-18.3, -5.7)	28.7(-4.8, 62.1)
Clinical volume (per 1000)		
Parameter estimate	0.7(0.3, 1.2)	0.6(0.2, 1.0)
Practice setting		
Non-rostered practice	-3(-5.8, -0.2)	-0.8(-3.0, 1.4)
Rostered practice	Ref	Ref
Other	-7(-11.2, -2.8)	-7.1(-11.6, -2.5)
Physician sex		
Female	Ref	Ref
Male	1(-1.8, 3.8)	-0.6(2.9, 1.6)
Missing	-16(-21.2, -10.8)	.

[†]Adjusted for all other variables

[*] Co-morbidity was evaluated using the Johns Hopkins Aggregated Diagnosis Groups (ADGs). Each ADG represents one cluster of disease with similar clinical criteria and expected needs for health care.

[**] Preventive service index score was calculated as the proportion of preventive services used out of the total number of preventive services for which an individual was eligible

Figure 6-1: A conceptual framework adapted from the Chronic Care Model

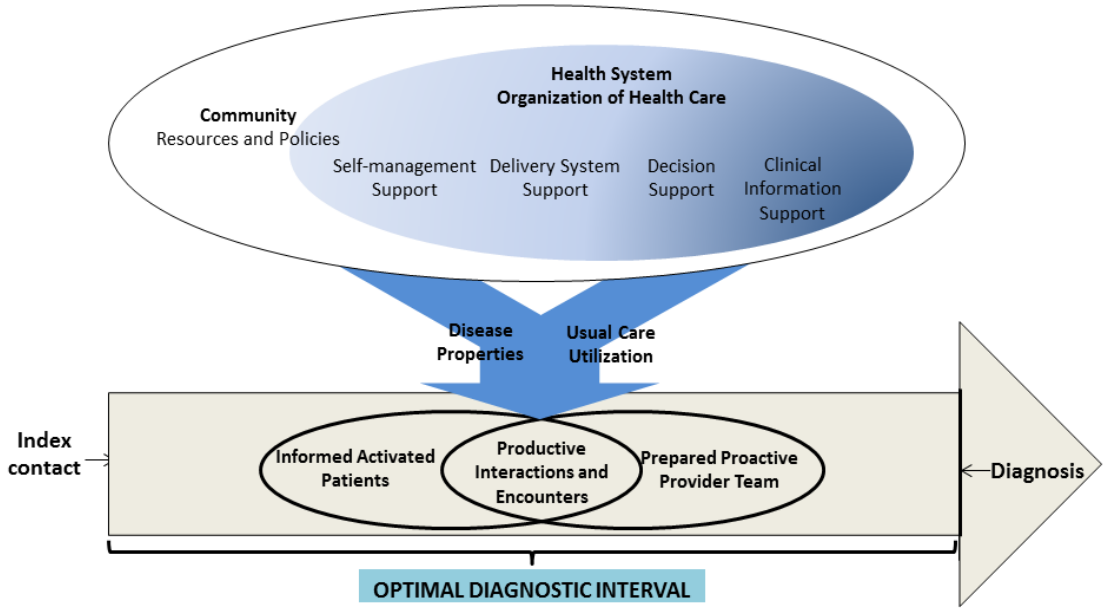
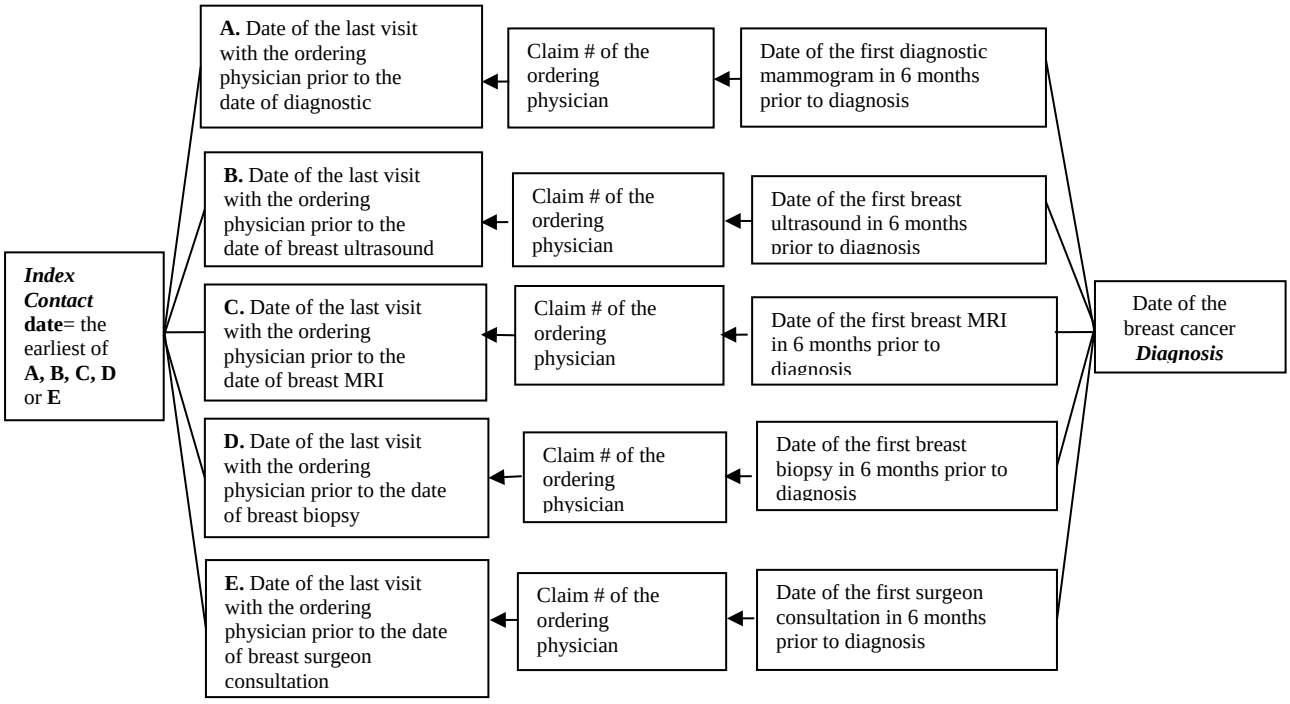


Figure 6-2: Working definition of the diagnostic interval



Chapter 7

General Discussion and Conclusions

7.1 Summary of Study Objectives and Key Findings

A total of 7830 breast cancer patients met the study eligibility criteria and 6898 of these patients had complete enough information to be included in the analyses. Of these, 2499 (36.2%) breast cancer patients were detected by screening and 4399 (63.8%) presented with signs or symptoms.

The analysis related to Objective 1 included all breast cancer patients with complete information for analyses (n=6898). The median time to diagnosis was 4.6 weeks (32 days). Forty-eight percent of breast cancer patients were diagnosed through a DAU and fifty-two percent were diagnosed through the usual care route (UC). Sixty-eight percent of breast cancer patients were diagnosed within targeted 7 weeks, with a significantly higher rate in DAU patients than that in UC patients (74.6% vs. 62.4%). Considerable variations in the diagnostic interval and DAU coverage were observed across Ontario counties, with the median diagnostic interval ranging from 2.1 weeks (15 days) to 9.3 weeks (65 days) and the DAU coverage rates ranging from 0 to 100%. The median diagnostic interval was inversely correlated with the DAU coverage rate at a county level, suggesting that DAUs may be effective in shortening the diagnostic interval for breast cancer patients.

The analysis related to Objective 2 examined the association between DAU use and the length of the diagnostic interval in a cohort of 2499 breast cancer patients whose disease was detected by screening. The median diagnostic interval was 4.1 weeks and 51.4% of screen-detected breast cancer patients were diagnosed through a DAU. DAUs had a higher rate in achieving the Canadian timeliness targets compared to usual care (79.1% vs. 70.2%). DAU use was significantly associated with an 8.3-day decrease in the diagnostic interval, adjusting for

potential confounders. These demonstrated that DAUs can improve the timeliness of abnormal screening follow-up for Ontario breast cancer patients.

The analysis related to Objective 3 examined the association between DAU use and the length of the diagnostic interval in a cohort of symptomatic breast cancer patients whose disease was not presented through an emergency department (n=4381). The median diagnostic interval was 4.9 weeks and 46.7% of symptomatic breast cancer patients were diagnosed through a DAU. Overall, 64.5% of patients met the 7-week target. Patients diagnosed in DAUs were more likely to achieve the Canadian timeliness target than those in UC (71.7% vs. 58.1%). Compared to usual care, DAUs significantly reduced the time to diagnosis by 9.9 days while controlling for potential confounders. These results provide the evidence base that Ontario DAUs significantly reduce the diagnostic interval for symptomatic breast cancer patients.

In summary, our study demonstrated that use of Ontario DAUs was associated with improved diagnostic timeliness for breast cancer patients, for both screening and symptomatic populations.

7.2 Discussion

The split of breast cancer patients by the method of cancer detection (screen-detected vs. symptomatic) was decided *a priori*. Previous evidence suggests that the method of cancer detection is an effect modifier of the association between many other factors and the length of the diagnostic interval (11;29;31). The association between DAU use and the length of the diagnostic interval was assumed to differ by the method of cancer detection, as we expected different diagnostic pathways for screen-detected patients and symptomatic patients. We therefore built two different models for screen-detected patients and symptomatic patients, with the former not controlling for referring physicians' characteristics. This is because the OBSP does not require a referring physician except for the initial screening and some OBSP screening centres directly arrange diagnostic assessment without re-referral from family doctors (90). In addition, the health

system organizes these two groups differently. While the OBSP monitors the timeliness of abnormal screening follow-up and has mechanisms to achieve national timeliness targets, the diagnostic experience of symptomatic patients is not formally tracked and assessed by the system. Thus, we thought that separate situation-specific recommendations would be more appropriate for knowledge translation purposes and applications of findings to policy development.

Both results of objective 2 and objective 3 demonstrated that DAU use was associated with an expedited diagnostic process for breast cancer patients but with slightly different effect sizes. DAUs tended to have a better performance in shortening the diagnostic interval for symptomatic patients than for screen-detected patients (9.9 days vs. 8.3 days). This difference may be explained by a more disadvantaged status of symptomatic patients than screen-detected patients in the usual care system, although this rather small difference could also have occurred by chance. The difference in the 90th percentile of the diagnostic interval between the symptomatic cohort and the screen-detected cohort was alarming (121 days vs. 79 days, respectively). Improved coordination of care through the organized screening program might explain this observed discrepancy.

7.3 Study Power

We could not estimate a minimum detectable time change in the median diagnostic interval between DAU and UC *a priori* because no previous study had used median regressions and thus the expected variation around the median was unknown. Post-hoc power calculations were performed separately for Objective 2 and Objective 3 to better understand the ability of this study to detect the observed differences in the median diagnostic interval between DAU and UC (see Appendix F). We had a 100% statistical power to observe an 8.3-day change in the median diagnostic interval for screen-detected breast cancer patients and had a 100% statistical power to detect a 10-day change in the median diagnostic interval in symptomatic breast cancer patients.

7.4 Study Strengths

Many strengths of this study are related to use of administrative databases. We were able to conduct a population-based study that covered the entire breast cancer population in Ontario during a one-year period. Previous studies that used administrative databases have demonstrated strengths in providing the population-based evidence base (13;16). In this study, use of population-based administrative data allowed us to extend beyond the organized breast screening program to include symptomatic breast cancer patients and those patients whose breast cancer was detected by the opportunistic screening, and thus the study results have good generalizability. Also, the large study sample size provided sufficient statistical power to detect relatively small differences. The administrative databases available to us contain a wide range of information on population and demographics, care providers, health services, cohort and registry, and cancer characteristics. This allowed us to measure and control for a number of potential confounders. The quality of the data used in this study is generally high, as previously described in the methods chapter with many of our key data elements having been validated and demonstrated to be concordant with clinical data in re-abstraction studies (170;171;174;178;180). In addition, the measurement of study variables using administrative databases was free from recall bias, which is a limitation of diagnostic delay studies that use patient self-report (6;257). Finally, this study was efficient as it used existing data.

The study also has several strengths related to its design. First, a retrospective cohort study design ensures the temporality of the association between DAU use and the length of the diagnostics interval. This has been an improvement over previous cross-sectional studies which collected information on diagnostic interval and other factors while at the same time doing patient interviews (6;257). Second, a conceptual framework was used to understand the diagnostic interval and guide the study design. This framework informed the design of the study, suggesting risk factors for diagnostic delay which we controlled for while assessing the association between

DAU use and the length of the diagnostic interval. Third, this study took advantage of a natural experiment in which DAU use was largely determined by geography. Fourth, median regression modeling (228) was for the first time employed to study the breast cancer diagnostic interval, which was positively skewed (4;8;11) and thus not appropriate for linear regression modeling. Parameter estimates obtained from median regression were more statistically robust than those that could have been obtained from a log-transformed linear regression and easier to interpret and use for knowledge transfer purposes.

7.5 Study Limitations

Use of administrative databases also led to several limitations in this study. Firstly, we had to assume abnormal results for patients whose mammogram was only recorded in the OHIP claims. Our decision to use OHIP claim-based mammograms up to six months before the diagnosis was based on the evidence from the Canadian Partnership Against Cancer (145;146), results from other studies (189), and our own observations using the OBSP data (see Appendix B). But some of these may have been negative mammograms while other patients may have had their initial abnormal mammogram more than six months prior to the diagnosis. Secondly, the OHIP codes that enabled us to differentiate between the purposes of mammogram (screening vs. diagnostic) were introduced three months before the start of our study period, and thus they might not have been completely adopted at the time of our study. Thirdly, we did not have information on the initial patient-physician encounter for breast problems and we had to assume the most recent referring doctor visit prior to the first diagnostic procedure (ordered by that doctor) was breast-related. All those limitations had effects on the identification of the index contact, which determines the method of cancer detection and the length of the diagnostic interval. These might have decreased the accuracy of point estimates described in Objective 1 and biased the DAUs' effect in screen-detected patients and symptomatic patients. However, such influence was expected to be small because 1) the first two limitations only apply to a small group of patients

with OHIP screening records (n=566); 2) we estimated that less than 5% of OHIP screen-detected patients waited longer than 6 months before a diagnosis (see Appendix B); and 3) we saw a dramatic increase in the number of claims for OHIP screening mammograms starting from 2011 suggesting widespread adoption (258). Lastly, the study results were restricted to a cohort of breast cancer patients. Evidence suggests that women with invasive breast cancer get a quicker diagnosis compared to those with benign diseases (45;164). So we expected a longer diagnostic interval for patients without breast cancer. DAUs' effect observed in this study might not be generalizable to patients who had benign breast abnormalities.

There might be unaddressed confounding effects. Unmeasured factors such as disease symptoms, patient beliefs and fear coping abilities, and doctors' communication skills may have influenced the association between DAU use and the diagnostic interval. Of these, we were particularly concerned about effects of confounding by indication, which indicates a phenomenon that patients with symptoms highly indicative of cancer receive more medical attention from physicians and thus have a quicker diagnosis (123;124;259). Administrative data does not contain detailed clinical information and we were not able to assess the influence of clinical triage on DAUs' effect. Our observation that patients with an earlier stage waited longer supports the presence of confounding by indication in our data and the inclusion of stage in our multivariate model partially addressed this issue.

We may also have residual confounding in our estimates of the DAU effect due to the imperfect measurement of study covariates. Some measurement errors may be related to the study methods, while some may be related to the accuracy of data sources. Our method of assigning recent immigration status using OHIP registration date might have misclassified some Canadians who moved to Ontario from another province as recent immigrants. Our method of identifying the referring physician may also have limited the accuracy in the measurement of referring physicians' characteristics. We were conservative in identifying the index contact and thus the

identified physician might be part of the diagnostic process rather than the person who initiated the diagnostic work-up. Therefore, we might have characterized some physicians as a referring physician when they were not. In addition, random coding errors and missing data may have affected the quality of the measurement of covariates. We think that all of these measurement errors were likely to be non-differential between DAU and UC, therefore, biasing DAU's effects towards the null.

A further limitation of this study was related to the determination of DAU use. We used a hierarchy to determine the diagnostic route (DAU vs. UC) based on the best available information. BAA use for patients detected by OBSP screening was expected to be accurate, since OBSP had a separate database tracking patients diagnosed at a BBA for payment purposes. DAU use for the rest of breast cancer patients was determined by comparing the diagnostic hospital with lists of DAU hospitals (see Appendix C). A cross-tabulation of the diagnostic-hospital approach and the BAA-payment approach revealed a high agreement between these two methodologies (see Appendix C). This non-differential misclassification might have biased the DAUs' effects towards the null. Additionally, results of our survey for regional breast assessment centres might not have provided a comprehensive list of such facilities. It is likely that we missed some regional DAUs and misclassified them as UC. Again, this misclassification would have reduced the difference between DAU and UC, thereby decreasing the effect size of DAUs.

We could not examine the regional impact of DAUs at a county level due to small numbers. Similarly, small county sample sizes restricted our ability to examine the DAUs' effects separately for screen-detected breast cancer patients and symptomatic breast cancer patients at a county level. We lost some breast cancer patients with missing information on the index contact (n=271, 3.4%) or DAU use (n=661, 8.4%). Since the number of patients without the DAU information was small (n=53) in the screen-detected cohort, we did not compare their characteristics with the rest of the screen-detected patients. We compared characteristics of the

608 patients whose DAU use information was unavailable with the rest of the symptomatic patients and found the former were slightly more likely to live in the urban area and were more likely to have Stage III-IV cancer. Exclusion of this group might have overestimated the length of the diagnostic interval and introduced bias to DAUs' effect.

7.6 Study Contribution

The Ontario DAUs have been in existence for nine years, but there is little knowledge of their population coverage and effectiveness in timely diagnosis outside the organized screening program. This thesis for the first time included symptomatic breast cancer patients and patients whose breast cancer was detected by opportunistic screening and provided population-level information on the length of the diagnostic interval and its association with DAU use among Ontario breast cancer patients. We provided the first empirical evidence that DAUs are more successful in meeting national timeliness targets and achieving timely diagnosis for both screen-detected and symptomatic patients, in the population of breast cancer patients. The effect sizes of DAUs were for the first time quantified in days, which provides an evidence base for future cost-effective studies. This thesis demonstrated considerable geographic variation in DAU use and the diagnostic interval and provided the first evidence to understand factors that might determine use of Ontario DAUs. The description of geographic variation in the diagnostic interval provides important information for policy-makers to compare currently achieved timeliness of diagnosis across regions and identify regions where specific interventions are needed. This information is also useful to evaluate the success of regional initiatives in improving the timeliness of diagnosis against stated targets. These observations provide important information for future system evaluation and program planning.

7.7 Public Health Implications and Future Research Direction

Results of this thesis have raised several public health concerns. First, early detection of breast cancer through screening tests was not achieved for the majority of breast cancer patients,

as only 36.2% were detected by screening. Among screen-eligible women (aged 50 to 69), over half of patients initially presented with signs/symptoms. Much more effort is needed to increase public awareness of early detection and the uptake of breast cancer screening tests. Second, considerable variation in the diagnostic interval has been observed provincially. For both screen-detected and symptomatic breast cancer patients, over thirty percent waited more than seven weeks (Canadian timeliness target) to get a cancer diagnosed. A small proportion of breast cancer patients had a diagnostic interval longer than three months, and such amount of delay can lead to a poorer survival based on the established evidence (23). Characteristics of these patients need to be understood to target specific interventions. Compared to screen-detected breast cancer patients, the 90th percentile of the diagnostic interval was much longer for symptomatic breast cancer patients (121 days vs. 79 days). Since most public health interventions have been focused on the organized breast screening program, more effort is needed to track the system performance and improve the diagnostic experience for patients outside the OBSP.

Study results suggested an association between DAU use and a shorter diagnostic interval in Ontario breast cancer patients. Compared to usual care, DAUs significantly reduced time to diagnosis by at least 8 days and appear to increase the rate in meeting the 7-week Canadian timeliness targets by at least 9% for both screen-detected and symptomatic breast cancer patients. These results generate important questions concerning the benefits associated with this amount of improvement in the timeliness of diagnosis. Although considerable qualitative evidence shows that a faster diagnosis can ease patient anxiety and distress during the diagnostic interval (22;130;140), there is no evidence so far suggesting that an 8-day decrease in the diagnostic interval affects clinical outcomes and there is little evidence to establish a standard benchmark for the clinically acceptable diagnostic interval (143;242). The current 7-week target is based on a review of existing guidelines, tumor progression and patient quality of care research (23;145). Future research is needed to understand the best achievable clinical practice and identify the

modifiable intervals for target setting purposes. The observation of geographic variation in the diagnostic interval across Ontario indicates that some areas had better practice and achieved more timely diagnosis than other areas. It is worth investigating factors that determine the length of diagnostic interval to understand reasons for this observed regional variation. Another important research direction is to understand the mechanism of DAUs in expediting the diagnostic process. DAUs have included multifaceted interventions to facilitate a faster diagnosis and achieve better quality of care. Identifying a specific component of the DAU that explains most of the DAUs' effect allows areas to achieve timely diagnosis in the absence of DAUs. This information is also important to develop evidence-based organizational standards that include the most effective component of DAUs while allowing for flexibility in the DAUs' structure based on the specific regional context. Lastly, DAUs also aim to provide better quality of care and better patient experience in addition to a rapid diagnosis. DAUs might also have advantages over UC in terms of easy access to care, patient support and quality of care (25;260). Therefore, a more comprehensive evaluation of DAUs' effect on patient satisfaction, quality of care, cost-effectiveness, and long-term clinical outcomes is warranted.

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Appendix A

Dataset Creation Plan

Name and Number of Study	Diagnostic Assessment Units' Impact on Diagnostic Delay: A Population-based study in Ontario, Canada (Project #: 2013 0800 142 000)
PI and P&B Contacts	Li Jiang, Patti Groome, Julie Gilbert, Hugh Langley, Marlo Whitehead.
Who will be responsible for DCP updates?	Li Jiang
PIA Approved?	Yes
DCP update history	Created Dec 15, 2012 Last updated July 24th , 2013

Short Description of Research Question

The diagnostic period in breast cancer is characterized by multiple appointments for diagnostic tests and consultations and it often provokes considerable distress and anxiety among women and their families. Delayed diagnosis is also associated with advanced cancer stage, aggressive treatment and poorer prognosis. In Ontario, efforts to achieve timely diagnosis have led to the development of the diagnostic assessment unit (DAU), which is an organizational structure designed to improve patient experience and quality of care through seamless transitions from abnormal detection to definitive diagnosis. However, the actual duration of diagnostic delay at the population level and the relative effectiveness of DAU versus usual care in achieving a timely diagnosis for breast cancer patients remain unclear. This study aimed to address these knowledge gaps and gain some insight into DAUs' performance in breast cancer.

Study Objectives:

2. To describe the length of the diagnostic interval and the DAU coverage in Ontario, and describe their geographic variations by county;
3. To examine the association between the DAU use and the length of the diagnostic interval in breast cancer patients detected by screening;
4. To examine the association between the DAU use and the length of the diagnostic interval in symptomatic breast cancer patients.

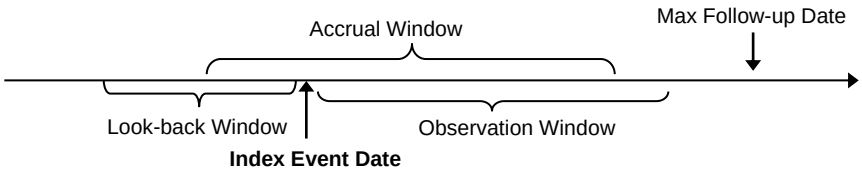
List of Datasets Used	***ICES:*** RPDB , CIHI/DAD (2007-2011), OHIP (1998-2011), OCR (2008- latest), IPDB, CAPE, OBSP (SCREENING entity, 2009- latest), NACRS (2007-2011), SDS (2007-2011) ***Cancer Care Ontario:*** OBSP (SCREEN, CLIENT entities) (Jan 1, 2009- latest) Stage Capture Project (Jan 1, 2011- latest)

Defining the Cohort

Index Event	Diagnosis of a single, primary invasive breast cancer between Jan 1st, 2011 and Dec 31st, 2011 (from the OCR)

	- *dxcode*= 174.0 to 174.9 (ICD-9)
Inclusions	Females (*sex* from the RPDB data); *n_prim*=1 (single, primary cancer); Histologically confirmed breast cancer; (n=8720)
Exclusions **(In order)**	- From the OCR data, exclude those patients: 1) Diagnosed at death certificate only (i.e. *bestsource*=D or *dxconfirm*=A or *dxdate* = 'date equal to or later than *Dodeath'*); (n=0) 2) Living outside of Ontario at the time of diagnosis (i.e. *the first letter of FSA ≠'K, L, M, N or P'*) (n=674) - From RPDB/CONTACT data, exclude patients: 3) who did not have OHIP coverage three years prior to diagnosis (for the purpose of measuring usual health utilization characteristics) (n=169)
Breast Cancer Cohort	Create a dataset for all eligible breast cancer patients;
Size of Cohort	N = 7830

Time Frame Definitions



Accrual Start/End Dates	Jan 1st, 2011 and Dec 31st , 2011
Max Follow-up Date	Dec 31st, 2011
When does observation window terminate?	Date of breast cancer diagnosis
Lookback Window(s)	36 months before the date of the breast cancer diagnosis (i.e. 3-year period) * look-back time was extended for preventive services variables (cancer screening)

Variable Definitions

Outcome Definitions	Diagnostic Interval: defined as the time interval between the index contact and the diagnosis date Strategy: With the exception for OBSP abnormal screening mammograms (look back 12 months), please work backwards **6 months** from the date of diagnosis (**include** the date of diagnosis) to identify OHIP screening tests and various breast diagnostic procedures and referral visits in the OBSP, OHIP, CIHI/DAD and SDS data (Please see Figure A-1) i. **Screening tests** • From the OBSP SCREEN* data, get the earliest abnormal screening record within 12 months before diagnosis date

where *screened* = 2 (mammogram only) **or** 3 (yes, both PE and mammogram) **and** finalres= C (breast cancer)

- From the OHIP data, get the earliest screening mammogram within 6 months prior to the diagnosis date (feecode: X172, X178)
- Find the earliest screening mammogram (label it as *date1*)

*Note: For the OBSP SCREEN subset, please get the variables "proctype" and "scrntype" for the purpose of identifying high-risk screenings.

ii. **Diagnostic investigations**

- from the OHIP, CIHI/DAD and SDS data, get all breast diagnostic procedures in the defined period of time
- Find the very first investigation for each diagnostic modalities (i.e. mammogram, ultrasound, MRI etc.) starting from 6-month prior and moving towards diagnosis.
- Identify the physician who ordered that very first assessment
- identify the last visit with that ordering physician for each breast diagnostic modalities;
- Find the earliest visit among all diagnostic routes (label the date of visit as *date2*)

iii. **ED-visits**

- From NACRS-ED visits data, get all breast-related ED visits during the defined period of time (i.e. *dx10code* or *eddischdx1*= "breast cancer (refer to Table A-1)", keep= *regdate*)
- Create a new variable called *date3=" the earliest date of breast-related ED visits"*

Please assign the Index contact date using a priority order as indicated below.

1) If the patient **ever** had a screening identified in step i), regardless of the order of other diagnostic procedures, assign index contact as the date of the earliest screening mammogram.
2) Otherwise, assign index contact as the date of the earliest diagnostic investigation identified in step ii) or earliest ED-vFigurisit identified in step iii), whichever occurred first.

Please create a variable called *referring_phys* ="*physnum* of the physician at the index contact"

Main Exposure or Risk Factor	Diagnostic Assessment Unit (DAU) status [Variable *DAU_status*= Yes/No] 1. Identify all biopsy/surgery procedures with non-missing hospitals for all patients from the OHIP, NACRS, CIHI-DAD and SDS data during the 6-month look back period including the diagnosis date (see procedure codes in Table A-2). 2. Identify the hospital where the biopsy/operation was performed closest to the diagnosis date 3. Please get the following variables from the OBSP SCREEN data (CCO) and link them to my dataset *ASSPAYMENTDT;*

	SIGNOFFFORPAYMENT;
Patients' Characteristics	1. Residence (variable: *county*) 2. Age at diagnosis (Variable: *age*) 3. Recent immigrant status (within ten years) [YES/NO, (1/0)] - Create a new variable called *Contact_10record* - Assign values to *contact_10record* using SAS macro. 4. Area-level material deprivation (variable: *Depr_index* (based on Dissemination Area)) - Please assign DA to each patient based on the most updated postal code - Link to Moineddin's look-up table using DA as a key 5. Urban/rural residence [Variable: *rio2008*] - Please create *rio2008* using SAS %getdemo macro 6. Co-morbidity (ADGs: Aggregated Diagnosis Groups) **within 36- and 12-months** before the date of diagnosis - Create new variables *ADG1-ADG34* using diagnoses codes from the OHIP and CIHI-DAD data within 12- to 36-month look back window 7. Benign breast disease history [Variable: *benign_bd_history* Value=1/0] **within 48- and 12-month** before date of diagnosis ~ From OHIP, CIHI/DAD, SDS and NACRS databases - if patients had any diagnostic codes of benign breast disease (see Table A-1), please indicate value of *benign_bd_history= 1(YES);* - if else, please indicate value of *benign_bd_history = 0 (No)*
Cancer Characteristics	Please link following variables from CCO Collaborative Stage Data to my dataset 1. Histological grade of cancer [Variables: *CSSF7*] 2. Cancer stage [Variables:*DerivedAJCC7T, DerivedAJCC7TDes, Derived AJCC7N, DerivedAJCC7NDes, DerivedAJCC7M, DerivedAJCC7Mdes, DerivedAJCC7StGrp*] 3. The method of cancer detection- refer to the outcome measurement [variable: *dis_pres*] - assign *dis_pres= 1* if *index_contact*= "*date1*" *dis_pres= 2* if *index_contact*= "*date2*" *dis_pres= 3* if *index_contact*= "*date3*"
Referring Physician's Characteristics	Referring physician: Only defined for patients with *dis_pres= 2* (linked with IPDB using *index_contact* and *referring_phys*) 1. Age 2. Sex [Male/Female] 3. Years in Practice - get physician's year of graduation (keep=*gradyear*) 4. Specialty - get physician's specialty (keep = *mainspecialty*)

5. Clinical Volume
   - get physician's total number of visits (keep= *tot_visits*)
6. Practice Setting [Variable: *Prac_setting=0/1/2* Non-rostered practice/Rostered practice/other]
   - Check the existence of records in CAPE data (linked using *ikn, referring_phys, servdate* from index contact in OHIP data)
   - Please indicate *Prac_setting* = 2 (other) if *mainspecialty ≠ GP/FP*; *FP/Emergency Medicine; Emergency Medicine; Community Medicine;*
   - Please indicate *Prac_setting* =1 (Rostered practice) if
     i. *mainspecialty = GP/FP*; *FP/Emergency Medicine; Emergency Medicine; Community Medicine;* and
     ii. there was record in CAPE for the combination of *ikn* and *referring_phys* and
     iii. This combination at the date of *index_contact* was eligible for enrolment of CAPE [i.e. *index_contact* = "between date of *startcape* and *endcape"* or (*index_contact* was after *startcape and endcape* was missing)]
   - Otherwise, please indicate *Prac_setting*= 0 (Non-rostered practice)

Usual Care Utilization Characteristics

Usual care utilization time window- **12- and 36-months** before the date of diagnosis:

1. **Frequency of doctor visits in 12 to 36 months before date of diagnosis: [Variable: Encounters = Total # of encounters]**
   - *Total # of health care encounters = # of office-based visits + # of emergency department visits + # of hospital admissions*
   - Office-based visits: (i) Office; (ii) Home; (iii) Phone; (iv) Long-Term Care; (v) Undefined
     i. From OHIP data, %ohip_location macro to define the location of OHIP claims for 'Consultations and Visits' (from Section A of the OHIP Fee Schedule); identify claims where *location = office; home; phone; ltc; undefined* (*keep = ikn, physnum, servdate, feecode; keepextra = location)*
     ii. Aggregate all claims by the same physician provided to the same patient on the same day (i.e. count as one health care encounter) and count the number of unique encounters for all office-based visits
   - Emergency department visits:
     i. From NACRS data, use %*getnacrs* macro to get ED visits in the defined period of time (*keep = ikn, dx10code1, Eddischdx1, regnum, sequence, aminst, regdate, lefteddate)*
     ii. Aggregate all ER claims provided to the same patient on the same day (may be from multiple physicians) and count the number of unique ER visits
   - Hospital admissions:
     i. From CIHI-DAD/SDS data, use *epi* (i.e. episodes of care –

series of linked hospital admissions) to count the number of unique hospital admissions

2. **Primary care provider- in <u>12 to 36 months</u> before date of diagnosis [Variable: Primary_Care = 0/1]**

   - from CAPE and OHIP data,
     i. Primary Care= 1 if **either** of the following conditions was satisfied:
        - Patients were continuously enrolled in CAPE during defined period of time (i.e. the full three year look-back period)
        - [there is no records in CAPE or the woman did not have full CAPE coverage for the three years] **<u>and</u>** [patients had at least two visits to a same FP/GP or at least one visit to an FP/GP for an annual physical examination (A visit of annual health examination will be identified from OHIP data: *feecode*=A003 **<u>and</u>** *dxcode*=917)]

     ii. Otherwise, Primary Care= 0.

3. **Continuity of care – Usual Provider Continuity (UPC) Index – in <u>12 to 36 months</u> before index event: [Variable: UPC = Value between 0 and 1 or undefined]**

   - ***UPC* = n_i / *N***; only defined for individuals with <u>3 or more visits</u> (i.e. $N \geq 3$) in defined period of time

     i. **N = total number of visits** to a GP/FP or a specialist in the office, phone, home, LTC facility, or undefined
        - Include visits where the physicians identified in *physnum* or *refphys* (from OHIP data) have *mainspecialty = GP/FP*; *FP/Emergency Medicine; Emergency Medicine; Community Medicine* (from IPDB data)
        - Visits to a specialist are attributed to the GP/FP who referred the patient (included in UPC calculation)

     ii. **n_i = number of visits to the usual provider** in defined period of time; where the usual provider is the physician who provides greatest proportion of care
        - Visits to a specialist are attributed to the GP/FP who referred the patient (included in UPC calculation)

   - For patients with <u>less than 3 visits</u> (i.e. N<3) in the defined period of time <u>or</u>
     Individual without a usual care provider, they will be combined as a separate group for analyses.

Note: Look back windows for the use of preventive services variables (#4-8) include

a 12-month buffer added to the recommended intervals of use.

4. **Physical examination in 12 to 36 months before date of diagnosis:**

   [*Variables*: (1) Physical_Exam = Yes/No; (2) Exam_Count = # of physical exams]

   - From OHIP data, *feecode = A003 and dxcode = 917*

5. **Influenza vaccination in 12 to 36 months before index event:**

   [*Variables*: (1) Flu_Shot = Yes/No; (2) Flu_Count = # of flu vaccinations]

   - From OHIP data, if either:
     i. *feecode = G590 or G591 (in any month)*
     ii. *feecode = G538 or G539 (in Oct. and Nov. only)*

6. **Breast cancer screening (Mammography) in 12 to 48 months before date of diagnosis: [*Variables*: (1) Mammogram = Yes/No/Missing; (2) Mam_Count = # of mammograms; (3) Mam_Eligibility = duration of eligibility]**

   - For females who were aged 50 to 69 years at any time during the 36-month look back window – include a variable for duration of eligibility
   - Woman was screened, if either:
     i. From OBSP SCREEN data, *screened = 2 (mammogram only) or 3 (yes, both PE and mammogram)*
     ii. From OHIP data, *feecode = X172, X178*

7. **Cervical cancer screening (Pap test) in 12 to 60 months before date of diagnosis: [*Variables*: (1) Pap_Test = Yes/No/Hysterectomy/Missing; (2) Pap_Count = # of pap tests; (3) Pap_Eligible = duration of eligibility]**

   - For females who were aged 69 years or younger at any time during the 48-month look back window – include a variable for duration of eligibility
   - Woman was screened, if there is at least one of the following from OHIP data:
     i. *feecode = G365 or G394 and feesuff = A*
     ii. *feecode = E430*
     iii. *feecode = L812 or L713 or L733*
   - Exclusion: Females with a hysterectomy (ever prior to the lookback window)
     i. From OHIP data, *feecode = S810, S757, S758, S816, S710, S763, S762, S727, S765, S766, or S767*

8. **Colorectal cancer screening in look back window before date of diagnosis:**

   - For females who were aged 50 to 74 years at any time during the specified look back windows of each test – include a variable for duration of eligibility

- Individual was screened, if there is <u>at least one</u> of the following from OHIP data during the specified look back windows:
    i. **Fecal Occult Blood Test in <u>12 to 48 months</u> before date of diagnosis:**

    [*Variables*: (1) FOBT = Yes/No/Missing; (2) FOBT_Count = # of FOBTs; (3) FOBT_Eligible = duration of eligibility]
        - Fecal occult blood testing: *feecode = L181 or G004*
    ii. **Sigmoidoscopy or barium enema in <u>12 to 84 months</u> before index event:**

    [*Variables*: (1) Sigmoidoscopy = Yes/No/Missing; (2) Sigmoid_Count = # of sigmoidoscopies; (3) Enema = Yes/No/Missing; (4) Enema_Count = # of barium enemas; (5) SigEnema_Eligible = duration of eligibility]
        - Rigid sigmoidoscopy: *feecode = Z535 or Z536*
        - Flexible sigmoidoscopy: *feecode = Z555 (without E740, E741, E747, or E705 on the same day) or Z580*
        - Single contrast barium enema: *feecode = X112*
        - Double contrast barium enema: *feecode = X113*
    iii. **During <u>12 to 144 months</u> before the date of diagnosis:**

    [*Variables*: (1) Colonoscpy = Yes/No/Missing; (2) Colon_Count = # of colonoscopies; (3) Colon_Eligible = duration of eligibility]
        - Colonoscopy: *feecode = Z555 <u>plus one</u> of E740, E741, E747, E705 on the same day*

Outline of Analysis Plan

All the analyses will be stratified by the disease presentation, which is, descriptive statistics and analytic statistics will be given separately for screen-detected and symptomatic groups.

Objective 1: The length of diagnostic interval was described using median and inter-quartile range, as the literature suggests that its distribution is positively skewed. The coverage rates of DAU were described using proportions. Plots were generated to visualize the geographic variation of the diagnostic interval and the DAU coverage rates. Pearson Correlation Coefficient was computed and compared with zero to test the hypothesized inverse correlation.

Objective 2 & 3: Bivariate associations between covariates and the DAU access were examined. A two-independent-sample t-test or a Wilcoxon rank sum test was used to compare continuous variables between the DAU and the UC groups. Independent chi-square test was used to compare proportions of categorical variables between the DAU and the UC groups. The bivariate associations between the length of the diagnostic interval and the study covariates were examined through the use of the median regression. The linearity assumption for continuous variables was assessed using bivariate median regression to decide if a categorization was needed. We chose categories for the continuous variables that considered the size of the interval and the frequency of observations within each interval. Variables were kept as continuous if the linearity assumption was satisfied. Otherwise, a categorical form was more appropriate for multivariate regression analyses. A single-level multivariate regression model was used to investigate the association between the DAU access and the diagnostic interval while adjusting for confounders. All potential confounders that we previously described were included in the multivariate regression analyses.

Figure A-1

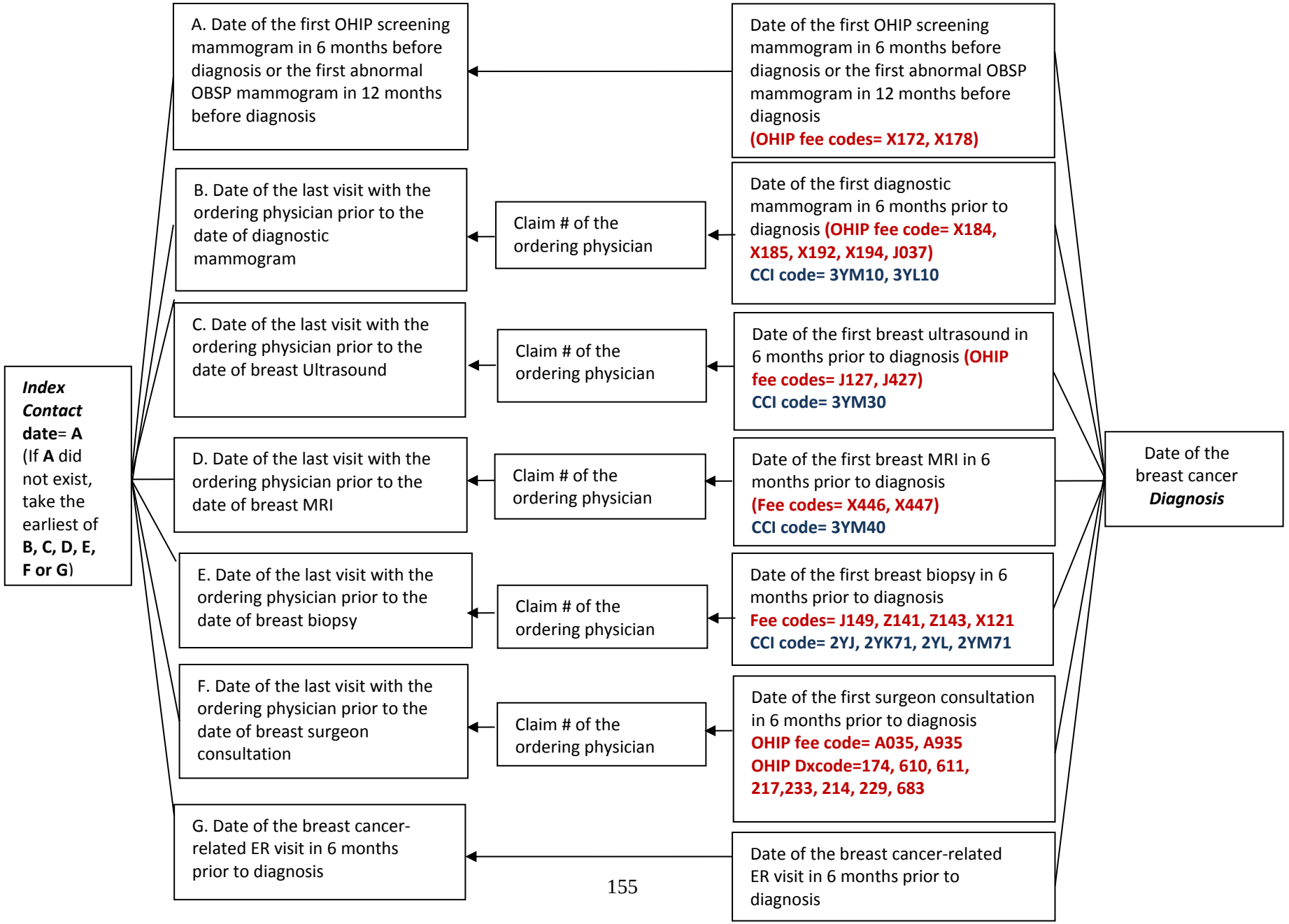

A. Date of the first OHIP screening mammogram in 6 months before diagnosis or the first abnormal OBSP mammogram in 12 months before diagnosis
B. Date of the last visit with the ordering physician prior to the date of diagnostic mammogram
C. Date of the last visit with the ordering physician prior to the date of breast Ultrasound
D. Date of the last visit with the ordering physician prior to the date of breast MRI
E. Date of the last visit with the ordering physician prior to the date of breast biopsy
F. Date of the last visit with the ordering physician prior to the date of breast surgeon consultation
G. Date of the breast cancer-related ER visit in 6 months prior to diagnosis
Index Contact date= A (If A did not exist, take the earliest of B, C, D, E, F or G)
Claim # of the ordering physician
Claim # of the ordering physician
Claim # of the ordering physician
Claim # of the ordering physician
Claim # of the ordering physician
Date of the first OHIP screening mammogram in 6 months before diagnosis or the first abnormal OBSP mammogram in 12 months before diagnosis (OHIP fee codes= X172, X178)
Date of the first diagnostic mammogram in 6 months prior to diagnosis (OHIP fee code= X184, X185, X192, X194, J037) CCI code= 3YM10, 3YL10
Date of the first breast ultrasound in 6 months prior to diagnosis (OHIP fee codes= J127, J427) CCI code= 3YM30
Date of the first breast MRI in 6 months prior to diagnosis (Fee codes= X446, X447) CCI code= 3YM40
Date of the first breast biopsy in 6 months prior to diagnosis Fee codes= J149, Z141, Z143, X121 CCI code= 2YJ, 2YK71, 2YL, 2YM71
Date of the first surgeon consultation in 6 months prior to diagnosis OHIP fee code= A035, A935 OHIP Dxcode=174, 610, 611, 217,233, 214, 229, 683
Date of the breast cancer-related ER visit in 6 months prior to diagnosis
Date of the breast cancer Diagnosis

Table A-1: Diagnostic codes

Disease	ICD-9 code (for OCR database)	OHIP dxcode (for OHIP database)	ICD-10 codes (for CIHI/DAD, SDS and NACRS databases)
Breast Cancer (Female)	174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.7, 174.8, 174.9	174	C50
Benign Breast Disease		610; 611; 217; 233	D24; N60; N61; N62; N63; N64

Table A-2: Breast-related procedure codes

Procedures	OHIP fee codes (for OHIP databases)	CCI codes (for CIHI/DAD, SDS and NACRS databases)
Screening Mammogram	X172, X178	
Diagnostic Procedures		
Diagnostic Mammogram	X184, X185, X192, X194, J037	3YM10, 3YL10
Diagnostic Ultrasound	J127, J427	3YM30
Diagnostic MRI	X446, X447	3YM40
Breast Biopsy	Z141, Z143, X121, R107, J149	2YJ, 2YK71, 2YL, 2YM71
General Surgical Consultation	A035, A935	
Therapeutic procedures		
Operation	E525, E526, R105, R108, R109, R111, R117	1YM87, 1YM88, 1YM89, 1YM90, 1YM91, 1YM92

Appendix B

Evidence Base for the study look-back time window

B-1: Observations in the OBSP data

The OBSP (SCREENING entity) Dataset provides final result of every OBSP screening test after completion of diagnostic assessment (1;2). Seven possible values for the variable 'finalres' were coded in the databases: B=Benign, N=Normal (mammogram was normal), O=Other cancer, C=Breast cancer, L=Concerning benign high risk lesion, U=Unknown/lost to follow-up, 'null'='woman is still undergoing breast assessment'. This information enabled us to identify OBSP screen-detected breast cancer patients because it represents the final decision made by the OBSP. We decided to look back 12 months for all OBSP screening test with a final result="C", based on Singh's work on diagnostic wait times in colorectal cancer (3) and expert opinions from Dr. Hugh Langley. We were able to describe the distribution of the length of the diagnostic interval using these OBSP screen-detected patients (Table B-1). Using a 12-month look back window, we found less than 5% of OBSP screen-detected patients had a diagnostic interval greater than 6 months (183 days). The number of screen-detected patients changed considerably in the table because of applying a hierarchy that assigned patients as screen-detected regardless of the order to other diagnostic tests.

Table B-1: Distribution of the length of diagnostic interval in OBSP screen-detected patients and OHIP screen-detected patients before and after applying a 6-month cut-off for the OHIP along with a hierarchy

	Screen type (look back time window)	***N***	***10th Q***	***25th Q***	***Median***	***75th Q***	***90th Q***	***95th Q***	***99th Q***
Before	OBSP (12-month)	905	10	19	35	58	91	114	244
	OHIP (12-month)	179	14	25	39	65	150	230	328
After	OBSP (12-month)	1986	10	17	29	50	80	102	211
	OHIP (6-month)	566	8	16	29	47	79	105	166

Note: All patients with complete information on the index contact date were included.

B-2: Other evidence

The Canadian Partnership Against Cancer published a report in which a 6-month look-back window was used to identify screen-detected cancer (4;5). Recently, Winget and colleagues (6) have compared two data sources in identifying the initial breast disease presentation (screening vs. symptomatic). They found the greatest concordance between administrative databases (without test results) and clinical data (with test results) when a 6-month look back window was used (7).

Appendix C

Determination of DAU use

C-1: List of BAA hospitals (matched with diagnosing hospitals in the study dataset)

BLUEWATER HEALTH-SARNIA GENERAL
CREDIT VALLEY HOSPITAL
GRAND RIVER HOSPITAL CORP-WATERLOO SITE
GREY BRUCE HEALTH SERVICES-OWEN SOUND
HAMILTON HEALTH SCIENCES CORP-JURAVINSKI
HAWKESBURY AND DISTRICT GENERAL HOSPITAL
HOSPITAL REGIONAL DE SUDBURY-LAURENTIAN
HOTEL DIEU HOSPITAL-KINGSTON
HOTEL-DIEU GRACE HOSPITAL-ST JOSEPH'S
LAKERIDGE HEALTH CORPORATION-BOWMANVILLE
LAKERIDGE HEALTH CORPORATION-OSHAWA SITE
LISTOWEL MEMORIAL HOSPITAL
MARKHAM STOUFFVILLE HOSPITAL
MOUNT SINAI HOSPITAL
NIAGARA HEALTH SYSTEM-GREATER NIAGARA
NIAGARA HEALTH SYSTEM-ST CATHARINES GEN
NIAGARA HEALTH SYSTEM-WELLAND COUNTY
OTTAWA HOSPITAL –CIVIC SITE
OTTAWA HOSPITAL –GENERAL SITE
PEMBROKE REGIONAL HOSPITAL INC.
PETERBOROUGH REGIONAL HEALTH CENTRE
PUBLIC GENERAL HOSP SOCIETY OF CHATHAM
QUINTE HEALTHCARE CORPORATION-BELLEVILLE
QUINTE HEALTHCARE CORPORATION-PICTON
QUINTE HEALTHCARE CORPORATION-TRENTON
RENFREW VICTORIA HOSPITAL
ROSS MEMORIAL HOSPITAL
ROUGE VALLEY HEALTH SYSTEM-CENTENARY

SAULT AREA HOSPITAL-SAULT STE MARIE
SCARBOROUGH HOSPITAL –SCAR.GEN.SITE
SOUTHLAKE REGIONAL HEALTH CENTRE
ST JOSEPH'S COMMUNITY HEALTH CENTRE
ST MICHAEL'S HOSPITAL
ST.JOSEPH'S HEALTH CARE, LONDON
STRATFORD GENERAL HOSPITAL
SUNNYBROOK HEALTH SCIENCES CENTRE
THUNDER BAY REGIONAL HLTH SCIENCES CTR
TIMMINS & DISTRICT GENERAL HOSPITAL
UNIVERSITY HEALTH NETWORK-PRINCESS MARG
WILLIAM OSLER HEALTH SYSTEM-BRAMPTON
WILLIAM OSLER HEALTH SYSTEM-ETOBICOKE
WINCHESTER DISTRICT MEMORIAL HOSPITAL
WINDSOR REGIONAL HOSPITAL-METROPOLITAN
WOMEN'S COLLEGE HOSPITAL
WOODSTOCK GENERAL HOSPITAL TRUST

C-2: List of regional breast assessment centres

We sent a survey to a total of 34 CCO Regional Primary Care Leads & the OBSP Regional Program Managers. The response rate of this three-round survey was 79.4% (27 responded). Of collected responses, we obtained 19 hospitals that were considered non-BAA DAUs during the year 2011. We excluded hospitals which were on the official list of BAAs provided by OBSP in 2011 (n=9). We also excluded hospitals that provided partial assessment, such as imaging and diagnostic ultrasound services (n=7), because DAUs were defined as facilities that were able to provide complete diagnostic assessment services in our thesis. The other reason for this exclusion was because we were not able to determine the use of partial assessment centres using administrative databases. Of remaining three hospitals, we were uncertain about the status of London Health Science Centre as a DAU. We made a conservative

decision to remove it from the list. Finally, we had two regional breast assessment centres/DAUs identified as follows:

NORTHUMBERLAND HILLS HOSPITAL
BROCKVILLE GENERAL HOSPITAL

C-3: Validation of the BAA determination using the OBSP payment records

OBSP tracks patients diagnosed through official BAAs for payment purposes. We cross-tabulated the determination of BAAs using our method of diagnosing hospitals and the BAA payment records (see Table C-1). Although the data quality of the OBSP payment records was unclear, we expected it to be highly reliable due to the payment purpose. We found our strategy had a sensitivity of 90.1% and a specificity of 84.6%, given the BAA payment records represent the truth.

Table C-1: Cross-tabulation of two different methods in BAAs determination

		BAA Payment Records	
		BAA=Yes (%)	**BAA=No (%)**
BAA determination using diagnosing hospitals	**BAA=Yes**	859 (90.1)	125(15.4)
	BAA=No	94 (9.9)	687(84.6)

C-4: Original list of BAAs provided by the OBSP

OBSP Site Name	City:	LHIN	Hospital or IHF	Assess-ment?	Assessment ONLY	Start Date: Assessment	End Date: Assess-ment
Bluewater Health Hospital	**Sarnia, 89 Norman Street, Level1 Sarnia, ON N7T 6S3**	01-Erie-St. Clair	Hosp	Y		**1-Jun-2011**	n/a
Breast Screening and Assessment Service OBSP Sudbury Regional Hospital	**Sudbury, 5th Floor, 865 Regent Street South**	13-North East	Hosp	Y		**1-Oct-2011**	n/a
Burlington Ultrasound and Radiology	**Burlington, 760 Brant Street, Suite 2 & 3 Burlington, ON L7R 4B8**	04-Hamilton Niagara Haldimand Brant	IHF	Y		**1-Feb-2008**	n/a
Chatham-Kent Health Alliance	**Chatham, 80 Grand Avenue West Chatham, ON N7L 1B7**	01-Erie-St. Clair	Hosp	Y		14-Oct-2005	n/a
Credit Valley Hospital	**Mississauga, 2200 Eglinton Avenue West Mississauga, ON L5M 2N1**	06-Mississauga Halton	Hosp	Y		19-Jan-2009	n/a
Dixie X-ray Associates Ltd - York-Finch Radiology (a.k.a. North York West Centre)	**Toronto (North York) - Downsview, 2065 Finch Avenue West, Ste. B1 Downsview, ON M3N 2V7**	08-Central	IHF	Y		10-Mar-2003	n/a
Grey Bruce Health Services	**Owen Sound, 1800 8th Street East, P.O. Box 1800 Owen Sound, ON N4K 6M9**	02-South West	Hosp	Y		20-Oct-2003	n/a
Hawkesbury - Breast Assessment Initiative Hopital General de Hawkesbury and District General Hospital Inc.	**Hawkesbury, 1111 Ghislain Street Hawkesbury, ON K6A 3G5**	11-Champlain	Hosp	Y		1-Jul-2008	n/a
Hotel-Dieu Grace Hospital	**Windsor, 1030 Ouellette Avenue Windsor, ON N9A 1E1**	01-Erie-St. Clair	Hosp	Y		4-Jan-2011	n/a
Hotel-Dieu Hospital	**Kingston, 166 Brock St., Kingston, ON K7L 5G2**	10-South East	Hosp	Y		1-Jul-2001	n/a
Juravinski Hospital Breast Assessment Affiliate	**Hamilton, 711 Concession Street East Hamilton, ON L8V 1C3**	04-Hamilton Niagara Haldimand Brant	Hosp	Y		30-Aug-2010	n/a
Lakeridge Health Corporation - Bowmanville Site	**Bowmanville, 47 Liberty Street Bowmanville, ON L1C 2N4**	09-Central East	Hosp	Y		29-Jan-2007	n/a
Lakeridge Health Corporation - Oshawa Site	**Oshawa, 1 Hospital Court Oshawa, ON L1G 2B9**	09-Central East	Hosp	Y		25-Sep-2006	n/a
Listowel Memorial Hospital	**Listowel, 255 Elizabeth Street East Listowel, ON N4W 2P5**	02-South West	Hosp	Y		**1-Nov-1999**	n/a
Markham Stouffville Hospital Corporation, Markham Site	**Markham, 381 Church Street Markham, ON L3P 7P3**	08-Central	Hosp	Y		17-Jan-2011	n/a
Markham Stouffville Hospital Corporation, Uxbridge Sites	**Uxbridge, 4 Campbell Drive Uxbridge, ON L9P 1S4**	09-Central East	Hosp	Y		17-Jan-2011	n/a

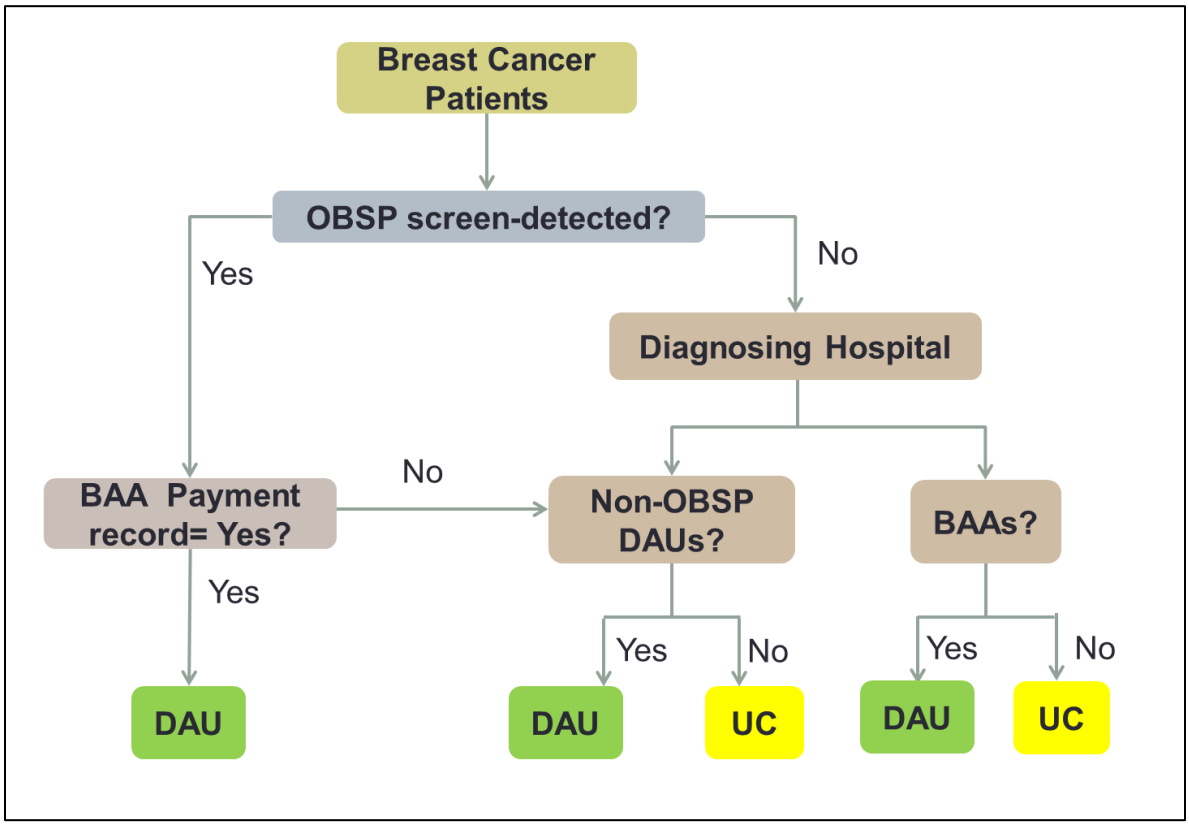
Mount Sinai Hospital	**Toronto, 600 University Avenue, 12th Floor Toronto, Ontario M5G 1X5**	07-Toronto Central	Hosp	Y		**14-Nov-2011**	n/a
Niagara Health System (NHS), Greater Niagara General Hospital	**Niagara Falls, 5546 Portage Road, P.O. Box 1018 Niagara Falls, ON L2E 6X2**	04-Hamilton Niagara Haldimand Brant	Hosp	Y		1-Apr-2002	n/a
Niagara Health System (NHS), St. Catharines General Hospital	**St. Catharines, 142 Queenston Street St. Catharines, ON L2R 7C6**	04-Hamilton Niagara Haldimand Brant	Hosp	Y		1-Apr-2002	n/a
Niagara Health System (NHS), Welland County General Hospital	**Welland, 65 Third Street Welland, ON L3B 4W6**	04-Hamilton Niagara Haldimand Brant	Hosp	Y		1-Apr-2002	n/a
Ottawa Regional Women's Breast Health Centre	**Ottawa, 1419 Carling Avenue, Suite 214 Hampton Park Plaza Ottawa, ON K1Z 7L6**	11-Champlain	Hosp	Y	**Y**	29-Oct-1998	n/a
Pembroke Regional Hospital	**Pembroke, 705 Mackay Street Pembroke, ON K8A 1G8**	11-Champlain	Hosp	Y		15-Mar-2002	n/a
Peterborough Regional Health Centre	**Peterborough, 1 Hospital Drive Peterborough, ON K9J 7C6**	09-Central East	Hosp	Y		**7-Jul-2011**	n/a
Port Perry Imaging	**Port Perry, 462 Paxton Street Port Perry, ON L9L 1L9**	09-Central East		N		1-Sep-2000	Jan/2005
Princess Margaret Hospital	**Toronto, 610 University Avenue, 3rd Fl Toronto, ON M5G 2M9**	07-Toronto Central	Hosp	Y		1-May-2006	n/a
Quinte Health Care Corporation Breast Assessment, Belleville Site	**Belleville**	10-South East	Hosp	Y		7-Sep-2010	n/a
Quinte Health Care Corporation Breast Assessment, Picton Site	**Picton**	10-South East	Hosp	N		7-Sep-2010	?
Quinte Health Care Corporation Breast Assessment, Trenton Site	**Trenton**	10-South East	Hosp	Y		7-Sep-2010	n/a
Renfrew Victoria Hospital	**Renfrew, 499 Raglan Street North Renfrew, ON K7V 1P6**	11-Champlain	Hosp	Y		1-Mar-2001	n/a
Ross Memorial Hospital	**Lindsay, 10 Angeline Street North Lindsay, ON K9V 4M8**	09-Central East	Hosp	Y		**1-Nov-2011**	n/a
Rouge Valley Health System, Centenary Stie	**Scarborough, 2867 Ellesmere Road Scarborough, ON M1E 4B9**	09-Central East	Hosp	Y		**1-Nov-2011**	
Sault Area Hospital	**Sault Ste Marie**	13-North East	Hosp	Y	**Y**	1-Apr-2009	n/a
Southlake Regional Health Centre	**Newmarket, 596 Davis Drive Newmarket, ON L3Y 2P9**	08-Central	Hosp	Y		**1-Nov-2011**	n/a

St. Joseph's Health Centre, London	**London, 268 Grosvenor Street London, ON N6A 4V2**	02-South West	Hosp	Y		1-Mar-2002	n/a
St. Joseph's Healthcare Hamilton, Centre for Ambulatory Health Services	**Hamilton, (St. Joseph's Healthcare Hamilton, King Campus) 2757 King Street East Hamilton, ON L8G 5E4**	04-Hamilton Niagara Haldimand Brant	Hosp	Y		20-Nov-2003	n/a
St. Michael's Hospital - CIBC Breast Centre	**Toronto, 30 Bond St, 3rd Fl, Queen Wing**	07-Toronto Central	Hosp	Y		1-Aug-2002	n/a
Stratford General Hospital	**Stratford, 46 General Hospital Drive Stratford, ON N5A 2Y6**	02-South West	Hosp	Y		25-Oct-2004	n/a
Sudbury Regional Breast Health Program	**Sudbury**	13-North East				15-Oct-2000	n/a
Sunnybrook Health Sciences Centre	**Toronto, 2075 Bayview Avenue Toronto, ON M4N 3M5**	07-Toronto Central	Hosp	Y		**4-Jul-2011**	n/a
The Scarborough Hospital, General Division	**Scarborough, 3050 Lawrence Ave. East Scarborough, ON M1P 2V5**	09-Central East	Hosp	Y		**15-Aug-2011**	n/a
Thunder Bay Regional Health Sciences Centre, Linda Buchan Centre	**Thunder Bay, 980 Oliver Road Thunder Bay, ON P7B 6V4**	14-North West	Hosp	Y		27-Mar-2006	n/a
Timmins and District Hospital	**Timmins**	13-North East	Hosp	Y		1-Jul-2011	n/a
Vaughan Imaging Consultants - Dixie X-Ray Associate Ltd.	**Woodbridge, 8333 Weston Road, Suite B04 Woodbridge, ON L4L 8E2**	08-Central	IHF	Y		13-Mar-2006	n/a
Victoria Hospital, London Health Sciences Centre	**London**	02-South West		N		2-Aug-2005	**Sep/2010**
Waterloo Wellington Breast Centre Freeport Health Centre, Grand River Hospital	**Kitchener, 3570 King Street East Kitchener, ON N2A 2W1**	03-Waterloo Wellington	Hosp	Y		30-Jul-2007	n/a
William Osler Health Centre, Brampton Civic Hospital	**Brampton, 2100 Bovaird Drive East Brampton, ON L6R 3J7**	05-Central West	Hosp	Y		**7-Nov-2011**	n/a
William Osler Health Centre, Etobicoke General Hospital	**Etobicoke, 89 Humber College Blvd. Suite 101 Etobicoke, ON M9V 1R8**	05-Central West	Hosp	Y		**7-Nov-2011**	n/a
Winchester District Memorial Hospital	**Winchester, 566 Louise Street Winchester, ON K0C 2K0**	11-Champlain	Hosp	Y		20-Jun-2003	n/a
Windsor Regional Hospital - Metropolitian Campus	**Windsor, 1995 Lens Avenue Windsor, ON N8W 1L9**	01-Erie-St. Clair	Hosp	Y		26-Jan-2004	n/a
Women's College Hospital	**Toronto, 76 Grenville Street, 7th Floor Toronto, ON M5S 1B2**	07-Toronto Central	Hosp	Y		**4-Jul-2011**	n/a

C-5: Final Algorithm in determining DAU use

The final algorithm in determining DAU use is displayed in Figure C-1.

Figure C-1: Algorithm of DAU/UC determination



Appendix D

Results for Assessment of the Linearity Assumption

The linearity assumption was examined separately in screen-detected patients and in symptomatic patients. Bivariate median regression was used to assess the assumption of linear association between the length of the diagnostic interval and continuous variables. Categories for the continuous variables were chosen based on the size of the interval as well as the frequency of observations within each interval (see Table D-1). Figure D-1 to Figure D-4 have shown the fit of categorized variables in bivariate median regression models in the screen-detected cohort, while Figure D-5 to Figure D-11 present the results in the symptomatic cohort. The length of diagnostic interval was plotted against the median value of independent variables within each interval, and a linear regression line was fit on each scatter plot to assess the linearity. Results showed that the categorized form of patient age, deprivation index, and the frequency of doctor visits and the continuous form of preventive service index were more appropriate for analyses in screen-detected patients, while categorization was only needed for patient age, deprivation index, and the referring physician's years in practice in symptomatic patients.

Table D-1: Categories and frequency distribution of continuous variables

	Screen-detected(N=2499)	***Symptomatic (N=4381)***
	N (%)	**N (%)**
Age		
<50	158(6.3)	1269(29.0)
50-59	783(31.3)	958(21.9)
60-69	953(38.1)	883(20.2)
70-79	498(19.9)	654(14.9)
80+	107(4.3)	617(14.1)
Deprivation index quintile		
1 (lowest)	656(29.8)	1135(29.2)
2	516(23.4)	857(22.1)
3	444(20.2)	738(19.0)
4	347(15.8)	629(16.1)
5 (highest)	239(10.9)	528(13.6)
missing	297	494
Frequency of doctor visits		
<10	980(39.2)	1772(40.5)
10-19	838(33.5)	1385(31.6)
20-29	391(15.7)	684(15.6)
30+	290(11.6)	540(12.3)
Preventive services index		
0	237(9.5)	779(17.8)
0<index< 50%	1114(44.6)	1695(38.7)
Index>=50%	1148(45.9)	1907(43.5)
Physician age		
<=45	NA	1088(25.3)
46-55		1353(31.5)
56-65		1337(31.0)
66+		523(12.2)
missing		80
Practice years		
<=20	NA	1246(29.1)
21-30		1407(32.8)
31-40		1164(27.1)
41+		471(11.0)
missing		93
Clinical Volume (per year)		
<4000	NA	1531(35.8)
4000-5999		1235(28.9)
6000-7999		688(16.1)
8000+		821(19.2)
missing		106

Figure D-1: The length of diagnostic interval by age (categorized variable) in bivariate median regression among screen-detected patients

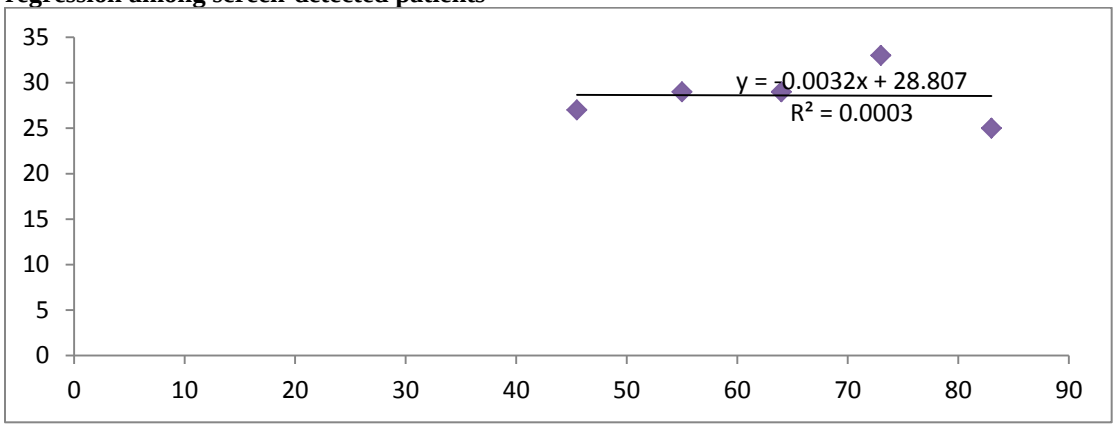


Figure D-2: The length of diagnostic interval by deprivation index (categorized variable) in bivariate median regression among screen-detected patients

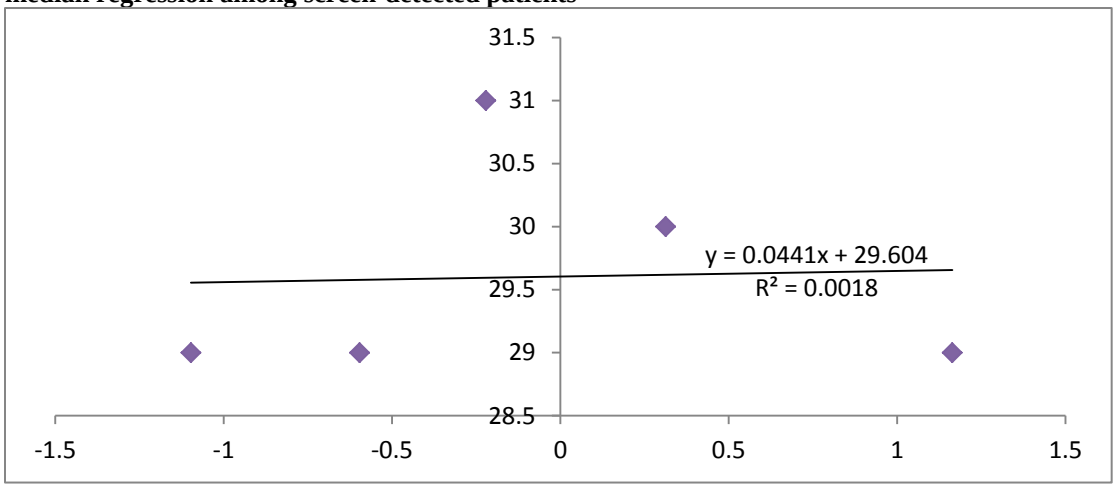


Figure D-3: The length of diagnostic interval by frequency of doctor visits (categorized variable) in bivariate median regression among screen-detected patients

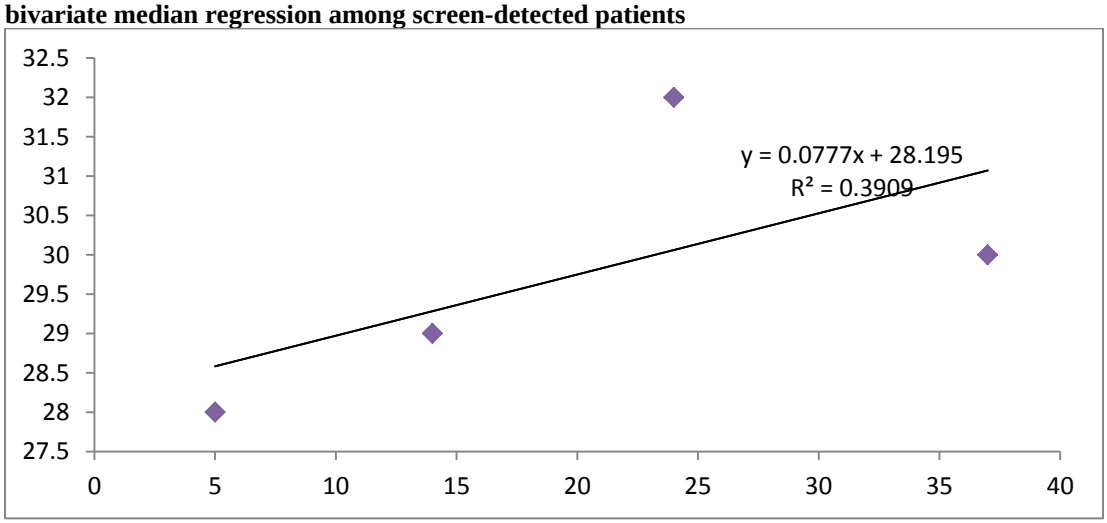


Figure D-4: The length of diagnostic interval by the preventive service index (categorized variable) in bivariate median regression among screen-detected patients

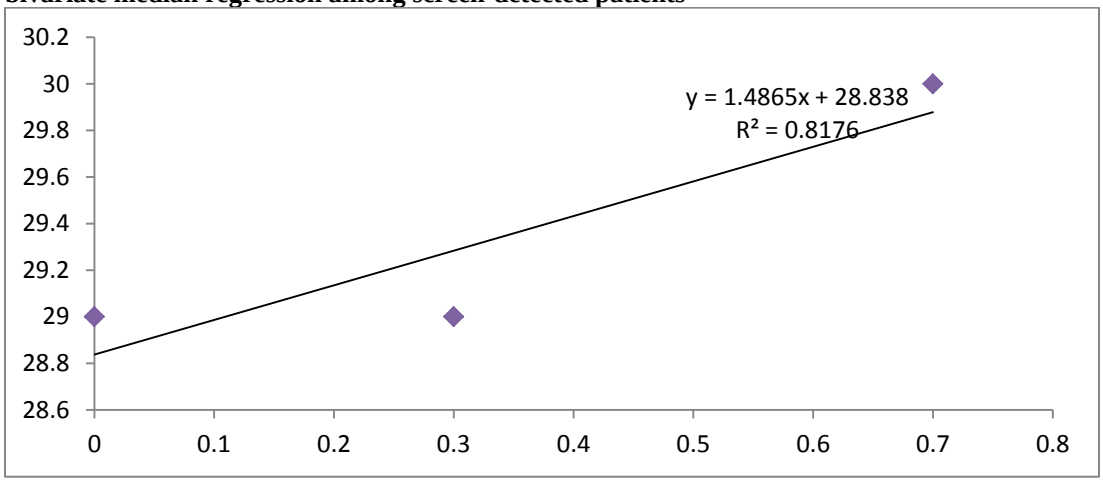


Figure D-5: The length of diagnostic interval by age (categorized variable) in bivariate median regression among symptomatic patients

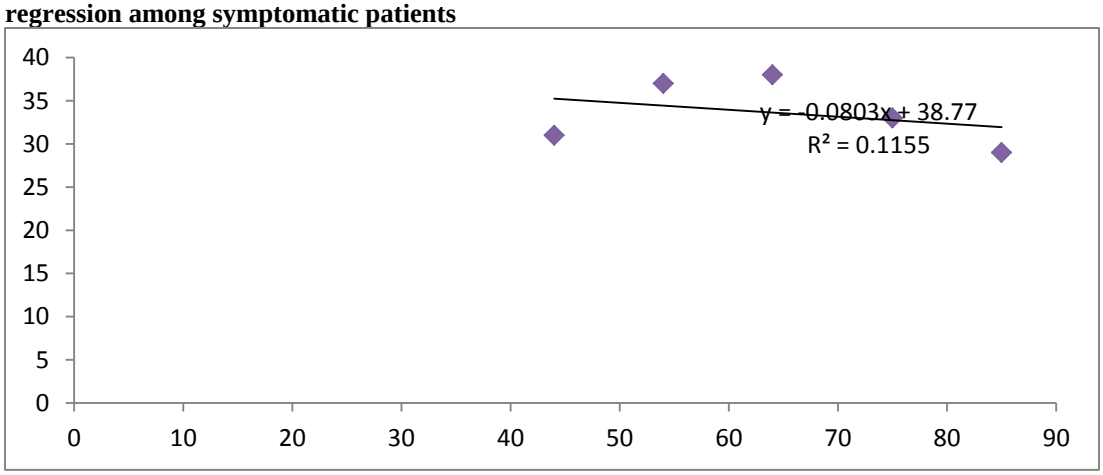


Figure D-6: The length of diagnostic interval by deprivation index (categorized variable) in bivariate median regression among symptomatic patients

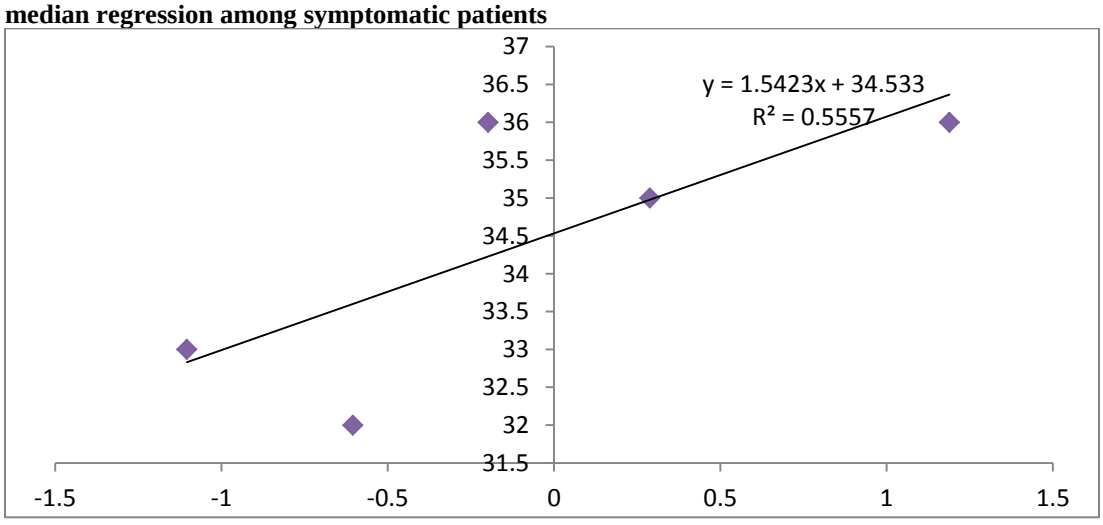


Figure D-7: The length of diagnostic interval by frequency of doctor visits (categorized variable) in bivariate median regression among symptomatic patients

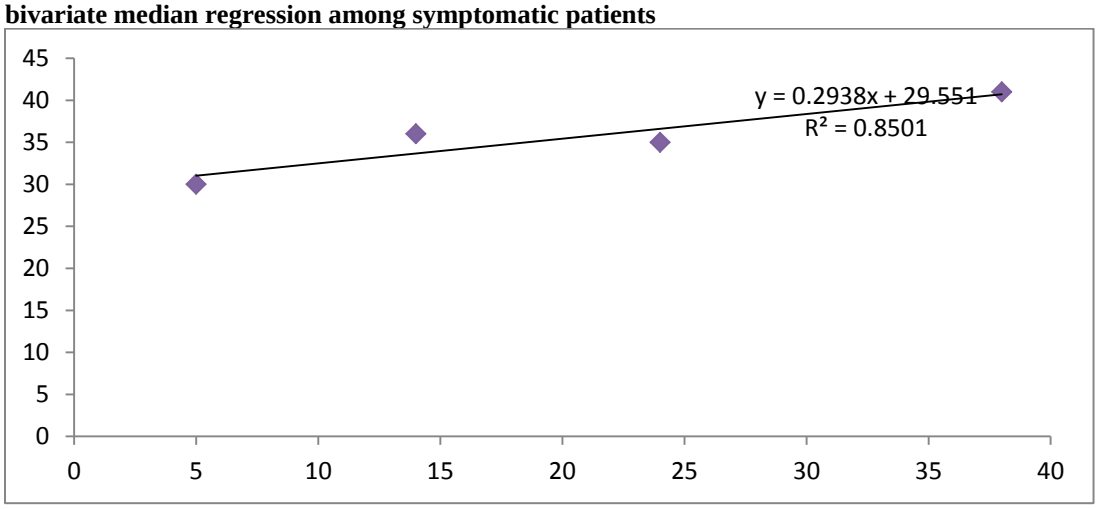


Figure D-8: The length of diagnostic interval by the preventive service index (categorized variable) in bivariate median regression among symptomatic patients

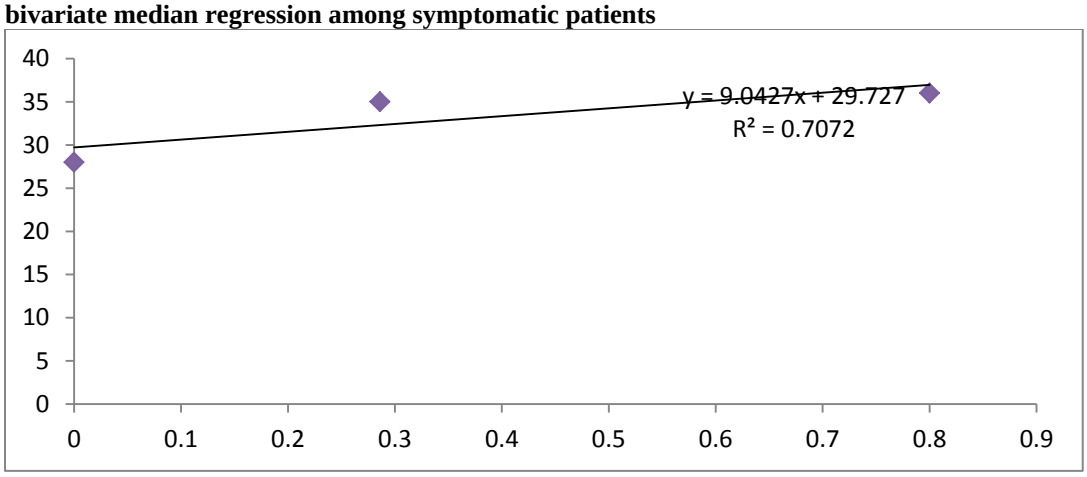


Figure D-9: The length of diagnostic interval by referring physician's age (categorized variable) in bivariate median regression among symptomatic patients

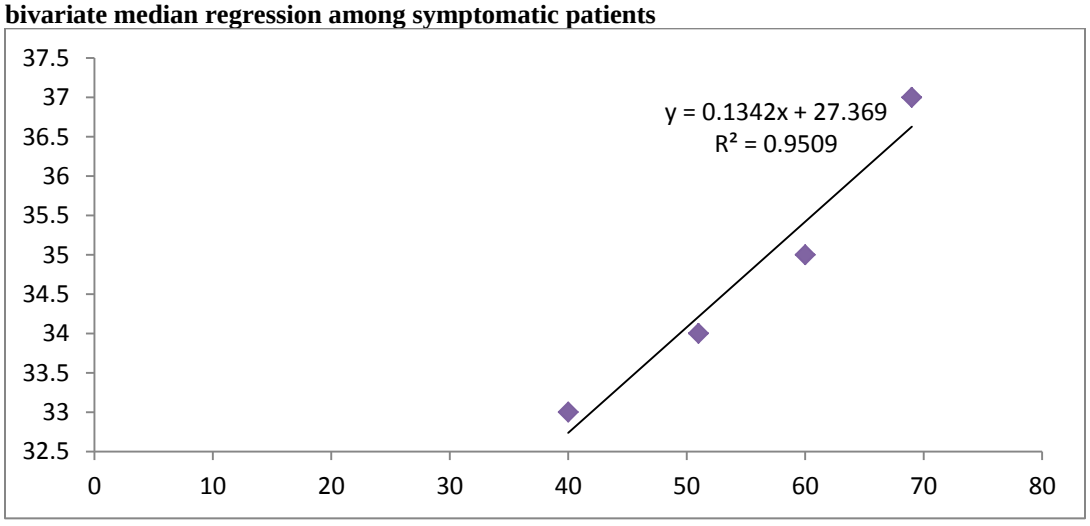


Figure D-10: The length of diagnostic interval by referring physicians' practice years (categorized variable) in bivariate median regression among symptomatic patients

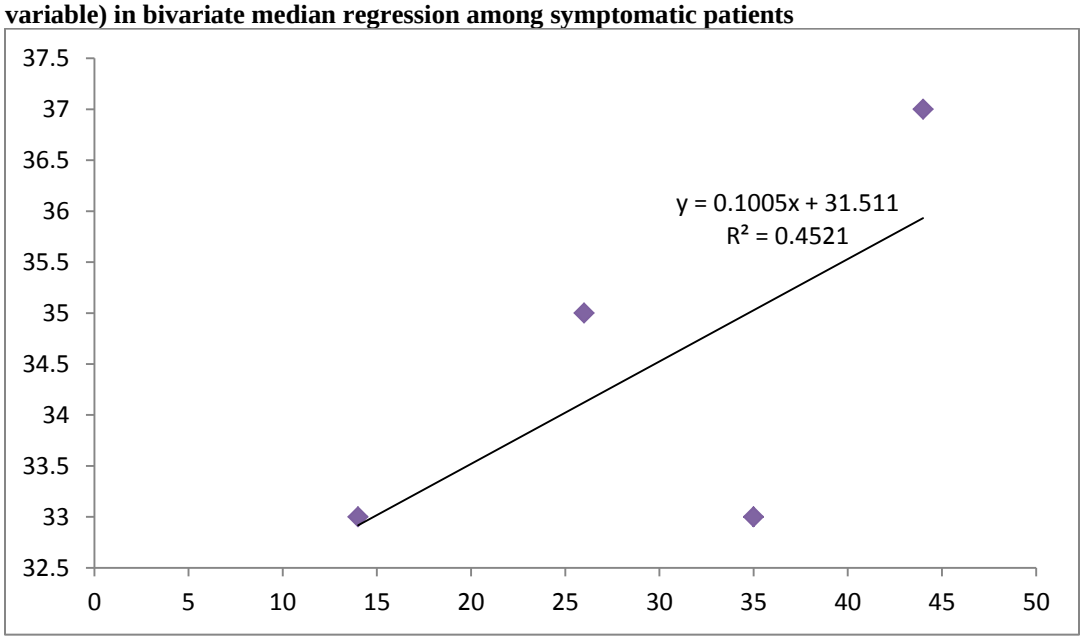
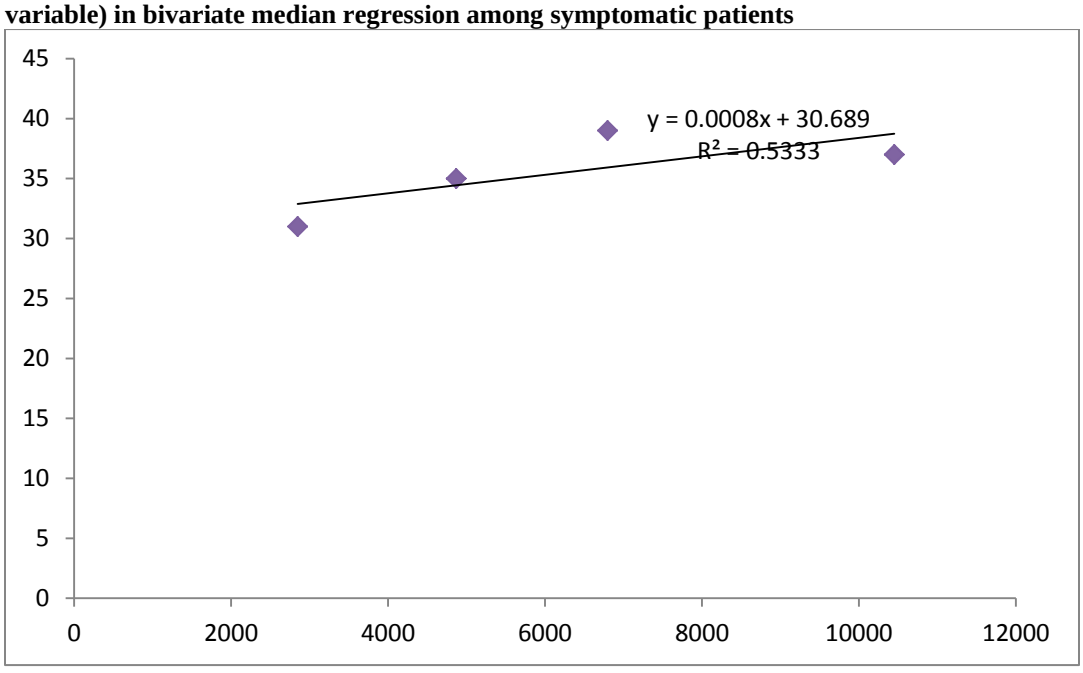


Figure D-11: The length of diagnostic interval by referring physicians' clinical volume (categorized variable) in bivariate median regression among symptomatic patients



Appendix E

Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
November 05, 2012

Miss Li Jiang
Department of Community Health and Epidemiology
Cancer Research Institute,
Queen's University

Dear Ms. Jiang
Study Title: EPID-400-12 Diagnostic Assessment Units' Impact on Diagnostic Delay in Breast Cancer: A Population-based Study in Ontario, Canada
File # 6007521
Co-Investigators: Dr. H. Langley, Dr. P. Groome, Dr. J. Gilbert, Ms. M. Whitehead

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol (October 2012) for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # **6007521** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6007521** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert J. Clark.

Chair, Research Ethics Board
November 05, 2012

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

Appendix F

Post-hoc Power Calculations

We calculated post-hoc study powers based on following information: 1) sample size 2) detected effect size (β1) 3) standard error of the effect size (β1) obtained from the median regression model using the bootstrapping method 4) a two-sided significance level of 0.5. Results of power calculations are presented in Table F-1.

Table F-1: Post-hoc power calculations for detected differences in diagnostic interval between DAUs and UC (two-sided)

	N	β_1	*S.E. of* β_1	α	*Power*
Screen-detected	2499	8.34	0.9545	0.05	100%
Symptomatic	4381	9.98	1.0460	0.05	100%

Appendices References

(1) Spencer N. Questions about coding in my requested datasets ID#12-115. Jiang L, editor. 6-12-2012.
Ref Type: Personal Communication

(2) Cancer Care Ontario. Cancer Care Ontario's Data Book-2012-2013. Cancer Care Ontario 2013 Available from: URL: https://www.cancercare.on.ca/ext/databook/db1213/whnjs.htm

(3) Singh H, De CC, Shu E, Fradette K, Latosinsky S, Pitz M, et al. Wait times from presentation to treatment for colorectal cancer: a population-based study. Can J Gastroenterol 2010 Jan;24(1):33-9.

(4) Canadian Partnership Against Cancer. Report from the Evaluation Indicators Working Group: Guidelines for Monitoring Breast Cancer Screening Program Performance. Toronto: Canadian Partnership Against Cancer; 2013.

(5) Canadian Partnership Against Cancer. Organized Breast Cancer Screening Programs in Canada: Report on Program Performance in 2007 and 2008. Toronto: Canadian Partnership Against Cancer; 2013 Feb.

(6) Winget M. Development of Methods to Evaluate the Pre-Diagnostic Breast Cancer Patient Trajectory Linking Existing Population-Level Databases. Cambridge 2013.

(7) Winget M. Question about screening mammogram. 6-11-2013.
Ref Type: Personal Communication