THE ASSOCIATION BETWEEN USUAL HEALTH CARE UTILIZATION AND STAGE AT DIAGNOSIS IN LARYNGEAL CANCER

By

Felicia Ga-Yin Leung

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ABSTRACT

Background: A significant number of laryngeal cancer patients are diagnosed with advanced-stage disease. Since stage at diagnosis is an important prognostic factor, it is necessary to understand the characteristics of individuals at risk of being diagnosed at an advanced stage.

Objectives: (1) Compare usual health care utilization between laryngeal cancer patients and the general population. (2) Evaluate the association between usual health care utilization and stage at diagnosis in laryngeal cancer.

Methods: The study population included 1,702 laryngeal cancer patients diagnosed from 2005–2008, and 8,510 matched-controls from the general population. Demographic, clinical, and health administrative data from Ontario were used to measure usual health care utilization in a two-year period (i.e. frequency of encounters, continuity of care, primary care model enrolment, and preventive services use), stage at diagnosis, and covariates.

Results: Laryngeal cancer patients had fewer health care encounters and a greater propensity for using preventive services than the general population. Comparisons of usual health care utilization among laryngeal cancer patients showed significant trends across Stage I–IV for the frequency of encounters (p=0.002), continuity of care (p=0.02), and preventive services use (p<0.0001). Stage I patients were less likely than Stage II–IV patients to have a low frequency of encounters (10%), low continuity of care (28%), and no preventive services use (28%). In adjusted multivariable analyses, low continuity of care was marginally associated with an increased risk of advanced-stage laryngeal cancer (RR [95% CI]: 1.17 [1.01, 1.34]). Stratification by subsite showed a marginally significant association between

continuity of care and stage in glottic cancer (RR [95% CI]: 1.25 [0.98, 1.58]), but no association in supraglottic cancer (RR [95% CI]: 1.01 [0.89, 1.15]).

Conclusions: Laryngeal cancer patients' patterns of usual health care utilization differ from the general population. There was little evidence of an effect of usual health care use on the risk of advanced-stage laryngeal cancer in multivariable analyses adjusting for confounders. Multinomial regression may be needed to fully elucidate the effects of health care utilization across Stage I–IV. Understanding health care utilization among laryngeal cancer patients is important for improving early detection and warrants further research.

CO-AUTHORSHIP

This thesis represents the work of Felicia G. Leung, which was completed in collaboration with her supervisors, Dr. Patti A. Groome and Dr. Stephen F. Hall.

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LIST OF ABBREVIATIONS

ACG	Adjusted Clinical Groups
ADG	Aggregated Diagnosis Group
AFP	Alternate funding plan
CCE	Division of Cancer Care and Epidemiology
CCO	Cancer Care Ontario
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
CSD	Census subdivision
GP/FP	General practitioner or family physician
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICES	Institute for Clinical Evaluative Sciences
IPDB	Institute for Clinical Evaluative Sciences Physicians Database
IQR	Interquartile range
LHIN	Local Health Integration Network
MOHLTC	Ministry of Health and Long-Term Care
OCR	Ontario Cancer Registry
OHIP	Ontario Health Insurance Plan
OPHRDC	Ontario Physician Human Resource Data Centre
OR	Odds ratio
RCC	Regional cancer centre
RIO	Rurality Index for Ontario
RPDB	Registered Persons Database
RR	Relative risk
SD	Standard deviation
subLHIN	subdivisions of Local Health Integration Network
TNM	Tumour, node, metastasis
UPC index	Usual Provider Continuity index

CHAPTER 1 INTRODUCTION

1.1 Background

Laryngeal cancers account for 0.7% of incident cancers in Canada, and are also the cause of 0.7% of cancer deaths (1). Over the past three decades, the incidence of laryngeal cancer has decreased significantly among males and females, which is largely attributed to declines in tobacco and alcohol use (1,2). A significant decrease in the mortality rates for males has also been observed since 2001 (1). However, the five-year relative survival rates for both supraglottic and glottic cancers have not improved over this time period (2).

A key prognostic factor for laryngeal cancer is disease stage at the time of diagnosis (3-5). In Ontario, the five-year overall survival rates for early-stage laryngeal cancer range from 69% to 78% (3,4). In contrast, the five-year overall survival rates are between 29% and 56% for advanced-stage laryngeal cancer (3,4). The distribution of stage at diagnosis varies significantly between the two major subsites of laryngeal cancer. Approximately 18% and 65% of patients in Ontario are diagnosed with advanced-stage glottic and supraglottic cancer, respectively (6). Aside from the location of laryngeal cancer, there are a number of other factors that have been hypothesized to contribute to variations in stage at diagnosis. Researchers have examined demographic characteristics, clinical factors, and diagnostic delay as predictors of the stage of laryngeal cancer diagnosis. The effect of health care utilization on stage at diagnosis has also been investigated in a few previous studies, which suggest that there is an association. Health care use is an important predictor of health outcomes; so understanding laryngeal cancer patients' usual health utilization will help elucidate reasons for advanced diagnoses.

1.2 Rationale

Laryngeal cancer can be extremely debilitating due to the loss of laryngeal function. The disease or subsequent treatments can impair speech and swallowing, which have a significant impact on patients' quality of life (4,7). Stage at diagnosis has been established as one of the most important prognostic factors for laryngeal cancer (5). However, a large proportion of laryngeal cancers are diagnosed at an advanced stage, despite being easily detected at an early stage during a clinical examination by an ear, nose, throat specialist (8,9). Understanding all of the patient- and system-related processes that contribute to an advanced diagnosis is important because early detection and diagnosis are integral components in the strategy to control laryngeal cancer. The current study aimed to provide insight into the usual patterns of pre-diagnostic health care utilization among laryngeal cancer patients with early- and advanced-stage disease. These characteristics can be useful for identifying individuals who are at risk of an advanced diagnosis of laryngeal cancer, as well as areas for improvement within the health care system, which can aid in reducing late diagnoses.

1.3 Study Objectives

The purpose of the study was to understand patterns of usual health care utilization among laryngeal cancer patients. The specific objectives of the study were:

1. To compare usual health care utilization between laryngeal cancer patients and the general population in Ontario; and,
2. To examine the associations between usual health care utilization prior to the diagnosis of laryngeal cancer and stage at diagnosis among patients in Ontario.

The primary focus of the research was Objective 2, while the purpose of Objective 1 was to provide a contextual description of laryngeal cancer patients' usual health care use relative to that of the general population.

1.4 Thesis Outline

The remainder of this thesis is organized into four sections. Chapter 2 presents a review of the literature on the epidemiology of laryngeal cancer, a conceptual model for understanding health care use and stage at diagnosis, factors that affect laryngeal cancer stage, and the characterization of health care utilization in health services research. In Chapter 3, an overview of the methods, including study design, data sources, study variables, and analytic strategies are described. The results of the statistical analyses for each study objective are presented in Chapter 4. Specifically described are comparisons of usual health care utilization between laryngeal cancer patients and the general population, as well as by stage at diagnosis among laryngeal cancer patients. Finally, Chapter 5 includes a discussion of the study findings within the context of previous literature. The strengths and limitations of the study, and the implications of the research are also addressed.

CHAPTER 2 BACKGROUND

2.1 Overview

This chapter presents a review of the literature that is relevant to the current study investigating the association between usual health care utilization and stage at diagnosis in laryngeal cancer. Firstly, a description of laryngeal cancer is provided. The next section describes a conceptual model that is used to study health care utilization and health outcomes. This is followed by a summary of the research on factors associated with stage at diagnosis of laryngeal cancer, which is presented within the context of the conceptual model. Next, literature on health care utilization in Canada is presented. Research on the effects of health care use on health outcomes is also presented, with a focus on outcomes related to cancer. The final section discusses the population health impact and the research gaps addressed by this research.

2.2 Laryngeal Cancer

2.2.1 Epidemiology

For 2011, it was estimated that 1,150 new cases of laryngeal cancer were diagnosed in Canada, which represented 0.7% of all incident cancers. The age-standardized incidence rate for laryngeal cancer in Canada was 3 per 100,000 (1). Laryngeal cancers accounted for 0.7% of cancer deaths in Canada, with 490 deaths expected in 2011 (1). Approximately 90% to 95% of laryngeal cancers are squamous cell carcinomas, which are classified into three anatomic sites: the supraglottis, the glottis, and the subglottis (10-14). Glottic cancers are the most prevalent and account for 59% of laryngeal cancers in Ontario, while 30% of laryngeal cancers arise in the supraglottis (15,16). In contrast, subglottic cancers are rare and represent 2% of laryngeal cancers, while 9% of laryngeal cancers are ill-defined (15,16). Laryngeal

cancers are diagnosed in males about four times more frequently than in females, where the typical age at diagnosis is between 50 and 70 years (10-14). Since the 1980's, significant decreases in the incidence of glottic and supraglottic cancers have been observed in the Canadian population (1,2). This trend may be explained by a simultaneous decline in the rates of tobacco and alcohol use (1,2). It is estimated that between 85% to 95% of laryngeal cancers can be directly attributed to smoking and alcohol consumption (10,11,17). Studies have established smoking as a primary cause of laryngeal cancer (10,11,13,17). Alcohol consumption has been identified as another independent risk factor, particularly for supraglottic cancer, which also acts synergistically with smoking (10,11,13,17).

2.2.2 Symptoms and Diagnosis

The symptoms of laryngeal cancer vary depending on the subsite and the extent of the tumour. Among glottic cancers, hoarseness is the predominant symptom and has been reported in 99% of cases (18-20). Hoarseness typically presents while glottic tumours are small because slight changes to the vocal cords will produce this symptom (10,18). In contrast, hoarseness becomes apparent when supraglottic tumours are more advanced. Although hoarseness is the most prevalent symptom, there is greater variation in the symptom profile of supraglottic cancer. Symptoms include sore throat, dysphagia, odynophagia, dyspnea, and otalgia (10,18). In addition, approximately 10% of patients with supraglottic cancer present with a neck mass. This is due to the rich lymphatic supply in the supraglottis compared to the glottis, which results in earlier nodal metastases (10,14,18). A diagnosis of laryngeal cancer is suspected if hoarseness persists for longer than two weeks or if dysphagia or odynophagia are present for six weeks or more, particularly if the patient has a history of smoking or alcohol use (10,12,13).

The variation in symptom presentation between subsites often results in an earlier diagnosis among patients with glottic cancer, while patients with supraglottic cancer are more frequently diagnosed at an advanced stage (10,14,18,19). The stage of laryngeal cancer is based on the tumour-node-metastasis (TNM) system and is determined through a combination of physical examination, laryngoscopy, biopsy, and diagnostic imaging (10,13,14,21). Increased tumour size with vocal cord fixation, nodal metastases in the neck, or distant metastases to the lung, mediastinum, liver, or bone indicates advanced-stage laryngeal cancer (i.e. Stage III or IV) and poor prognosis (13,14). The distribution of stage at diagnosis is significantly different between the two laryngeal cancer subsites, with 17.6% of glottic cancers diagnosed as advanced-stage disease compared to 65.2% of supraglottic cancers in Ontario (6).

2.2.3 Treatment and Prognosis

The aims of laryngeal cancer treatment are to cure the disease, while reducing morbidity and preserving laryngeal function where possible (11-13). Surgery and radiotherapy are the primary treatment modalities for glottic and supraglottic cancer. For early-stage laryngeal cancer, treatment with either surgery or radiation alone are the main treatment options, with the two modalities demonstrating comparable rates of control (12-14). Advanced-stage laryngeal cancer, on the other hand, is treated by combination-modality therapy using surgery and radiation. Recently, chemotherapy as a neoadjuvant or adjuvant therapy has become important for treating advanced laryngeal cancer in order to improve the chance of laryngeal preservation (12-14). However, treatment indications for advanced-stage laryngeal cancer are controversial due to variations in disease and patient characteristics, as well as the poor quality of evidence comparing treatment modalities (3,4).

In Ontario, the five-year overall survival rates for glottic cancers diagnosed between 1982 and 1995 were 78% for T1, 69% for T2, 47% for T3, and 33% for T4 disease (3). For supraglottic cancers diagnosed between 1982 and 1995, the five-year overall survival rates in Ontario were 74.3% for Stage I and Stage II, 55.7% for Stage III, and 28.5% for Stage IV disease (4). Based on these findings, it is apparent that patients diagnosed with early-stage laryngeal cancer have significantly better survival than those who present with advanced-stage disease. Although increased survival has been observed for other head and neck cancers since the 1980's, there is no evidence of improvements in five-year relative survival rates for either supraglottic or glottic cancer (2).

2.3 Conceptual Model of Health Care Utilization

Andersen's Behavioural Model of Health Services Use is a theoretical framework that is widely used in health services research to understand an individual's health care utilization and to examine access to health care. According to Andersen's model, health care utilization is the realized access of health services, while the presence of factors that enable health services use is defined as potential access (22). The framework proposed by Andersen and colleagues posits that an individual's use of health services is determined by three primary factors: predisposing characteristics, enabling factors, and the need for health care (22). Demographic factors, such as age, sex, ethnicity, marital status, and level of education, and health beliefs are considered to be predisposing characteristics because these are biological and social determinants of an individual's likelihood to seek health care and are not readily modified (22,23). Enabling factors refer to the personal and community resources that allow an individual to use health services. These include having financial resources, such as health insurance and income, as well as the availability of health care providers and facilities (22). The final determinant is an individual's need for health care, which

encompasses perceived and evaluated need. Perceived need is a crucial component for understanding health services use since an individual must assess his or her own health and decide whether or not to seek help. Evaluated need, on the other hand, is the health assessment by medical professionals and will determine the amount of health care required (22). Andersen's model also suggests that health care utilization affects health status and patient satisfaction, which can be used to evaluate the effectiveness and efficiency of health care access (22). Furthermore, this framework recognizes that there is feedback among predisposing, enabling, and need factors, health care use, and health outcomes (22).

2.4 Stage at Diagnosis of Laryngeal Cancer

Stage at the time of diagnosis has been established as a key prognostic factor for laryngeal cancer and there is evidence of an inverse relationship between stage and survival (3-5). Andersen's Behavioural Model of Health Care Use can be applied to understand factors that contribute to variations in stage at diagnosis, which is an important health outcome for laryngeal cancer patients. Based on this framework, stage at diagnosis is determined by predisposing characteristics, enabling factors, need for health care use, and health care utilization.

Figure 2-1 presents the conceptual model for understanding stage at diagnosis of laryngeal cancer and components of the model that have been studied to date. The predisposing factors that have been investigated include the following demographic characteristics: age, sex, and race. Alcohol and tobacco use are additional predisposing characteristics and also characterize individuals' need to use health services. Other population characteristics that have been examined in relation to the stage of laryngeal cancer are socioeconomic status, which is an enabling resource. Diagnostic delay, which reflects an enabling factor, and a perceived and evaluated need for health care, has also been studied. In

addition, studies have investigated the effect of the number of visits and continuity of care on stage at diagnosis of laryngeal cancer.

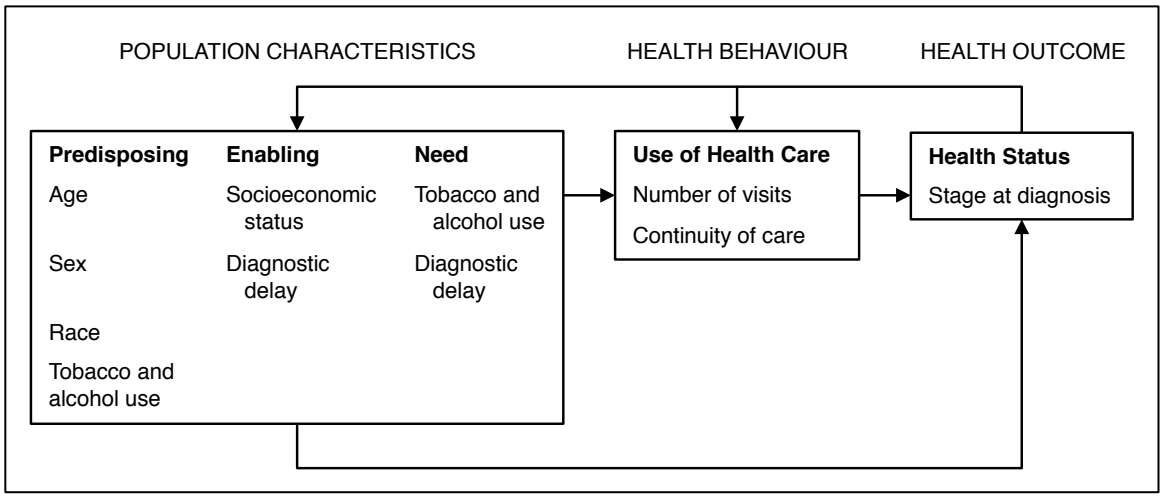

Figure 2-1. Conceptual model for stage at diagnosis of laryngeal cancer and factors that have been examined in the literature. Adapted from Andersen's Behavioural Model of Health Services Use (22).

2.4.1 Demographic Characteristics and Stage at Diagnosis

Age, sex, and race are biologic predisposing factors that have been examined for an association with stage at diagnosis of laryngeal cancer. Three studies reported that age was significantly associated with stage at diagnosis, with younger patients more likely to be diagnosed with advanced-stage disease (1-4). With regards to the effect of sex, a study of laryngeal cancer patients reported that males were less likely to have an advanced-stage cancer at diagnosis in comparison to females (24). However, there was no apparent association between sex and stage at diagnosis when all head and neck cancers (i.e. oral cavity, pharynx, and larynx) were studied (25-27). The inconsistent findings from these studies are likely due to the cancer sites that were included. Combining head and neck cancer sites may not be appropriate because sex-specific biological factors may have a differential effect on disease pathogenesis for different cancers. Race has also been found to be significantly associated with stage at diagnosis. For head and neck cancer, patients of

non-white race were more likely to be diagnosed with advanced-stage disease compared to patients of white race (26). Among laryngeal cancer patients, the odds of advanced-stage disease at diagnosis was 38% greater for African Americans than for whites (24).

2.4.2 Tobacco and Alcohol Use and Stage at Diagnosis

Within the conceptual model, the consumption of tobacco and alcohol is a predisposing characteristic because these health risk behaviours reflect an individual's health beliefs. Tobacco and alcohol use also measures health care need for laryngeal cancer risk awareness by both the patient and his or her doctor, since tobacco and alcohol use are the main risk factors for laryngeal cancer. Thus, it is important to understand how these patient characteristics affect the severity of the disease at diagnosis. Trigg et al. (28) found that tobacco and alcohol use were independently, significantly associated with advanced-stage laryngeal cancer. Although the size of the effects were moderate, the odds of being diagnosed with advanced-stage laryngeal cancer were increased for patients who used either tobacco or alcohol compared to those who abstained (28). Likewise, former smokers were shown to have a 67% reduction in the odds of advanced-stage head and neck cancer at diagnosis versus current smokers, although the decreased likelihood of advanced disease was not statistically significant for non-smokers (27). A study of head and neck cancer patients also reported that patients who abused alcohol and tobacco were more likely to be diagnosed with advanced-stage cancer than those who only used tobacco (29). This finding is consistent with the higher prevalence of advanced-stage disease in supraglottic cancer, since alcohol is a stronger risk factor for this subsite (17,30). The differential effect of risk factors on the laryngeal subsites is due to greater exposure to ingested substances (i.e. alcohol) in the supraglottis and more contact with inhaled substances (i.e. smoking) in the glottis (30). Interestingly, Reid et al. (26) found that head and neck cancer patients who had a diagnosis of

one or more alcohol- or tobacco-related co-morbidities were less likely to have an advanced-stage cancer diagnosis than patients without any of these co-morbid conditions. One explanation for this finding is that the study identified these co-morbidities from physician claims (26). Thus, patients with these co-morbidities have contacts with the health care system prior to cancer diagnosis and physicians may be likely to suspect laryngeal cancer in these patients.

2.4.3 Socioeconomic Status and Stage at Diagnosis

An important enabling factor is socioeconomic status, which affects an individual's ability to access health care. The relationship between socioeconomic status and stage at diagnosis has been of interest because it is a possible explanation for socioeconomic differences in cancer survival (31,32). Groome et al. (32) previously examined the effect of area-level socioeconomic status on cause-specific survival and local-regional failure for laryngeal cancer in Ontario. Although socioeconomic status was not associated with these outcomes for supraglottic cancer, the relationship was observed for glottic cancer and tumour stage at diagnosis explained between 3% and 23% of this association (32). However, two studies from Ontario which examined the direct relationship between socioeconomic status and stage of diagnosis in laryngeal cancer did not find a significant association (27,33). Neither education level nor median family income, which were an individual-level and an ecological measure of socioeconomic status, respectively, had an effect on stage in squamous cell carcinomas of the head and neck (27). Similarly, a population-based study by Booth et al. (33) showed that the distributions of Stage I and Stage IV disease at diagnosis for laryngeal cancer did not vary significantly between patients in the lowest neighbourhood median income quintile and individuals in the other four income quintiles. A possible explanation for the null findings of these two studies, compared to the socioeconomic effects observed by

Groome et al. (32), is that the studies did not differentiate the subsites of laryngeal cancer. This may have limited the studies' ability to detect an association between socioeconomic status and stage.

Studies from the United States, on the other hand, have found that socioeconomic status affects the stage of diagnosis in laryngeal cancer. Using cancer registry data, Greenlee et al. (34) found that there was a strong, positive, linear association between the proportion of laryngeal cancer patients diagnosed with distant disease and the degree of county-level poverty. The odds of distant-stage laryngeal cancer was significantly increased for patients living in counties with 10-19%, 20-29%, and 30+% below the poverty level compared to those from counties with <10% below poverty. The odds of being diagnosed with distant-stage laryngeal cancer was 2.38 times greater for persons in the highest poverty level than for those in the lowest poverty group (34). Interestingly, the association between area-level poverty and distant-stage laryngeal cancer was only observed for individuals who lived in metropolitan counties, but not for those living in non-metropolitan counties (34). For studies conducted in the United States, health insurance status is another measure used to characterize socioeconomic status (31). A study that investigated health insurance status and stage at diagnosis in laryngeal cancer found that the type of health insurance was strongly associated with having Stage III or IV disease. Patients who were uninsured or who had Medicaid coverage had 1.97 and 2.40 times the odds, respectively, of having advanced-stage laryngeal cancer compared to those who had private health insurance (24). This study also found that area-level measures of education and median household income were statistically associated with advanced stage, but these effects were not strong (24).

The varied results from these four studies may be attributed to differences in the study methods. Firstly, the two studies on laryngeal cancer patients in Ontario had considerably smaller sample sizes ($n \approx 160$ to 800) than the studies from the United States (n

≈ 25,000 to 51,000), which may have affected the power of the studies to detect an association, particularly if there are differences between subsites. Another key methodological difference that may explain the different findings is the measurement of socioeconomic status. Zhang-Salomons et al. (35) previously showed that the observed associations between socioeconomic status and health outcomes depend on the measure of socioeconomic status. Thus, the use of different socioeconomic status indicators in the four studies may have contributed to the inconsistent results. Additionally, in the study by Booth et al. (33), the dichotomization of neighbourhood median income quintile reduced the true variation of socioeconomic status, which could have obscured the association. Further research, with adequate study power and more consistent methodology, is needed to elucidate the relationship between socioeconomic status and stage at diagnosis in laryngeal cancer.

2.4.4 Diagnostic Delay and Stage at Diagnosis

Diagnostic delay is defined as the total length of time between the onset of symptoms and the definitive cancer diagnosis (36,37). The two stages of diagnostic delay are patient delay (i.e. time from symptom presentation to the first visit with a health care provider) and professional delay (i.e. period from the initial consultation with a health care provider to the confirmation of diagnosis by a specialist) (36,37). Within Andersen's model, diagnostic delay measures enabling factors and need for health care. Specifically, patient delay results from an absence of enabling resources, such as having a GP/FP or available time and transportation to attend an appointment (32). Patient delay also characterizes perceived need because an individual assesses the severity of his or her symptoms. Evaluated need is captured by professional delay, as the initial health care provider decides on the care that is required.

Studies have reported the median duration of total diagnostic delay to range from 108 to 201 days for glottic cancer, while the median length of total diagnostic delay for supraglottic cancer was between 120 and 156 days (18,20,38). In laryngeal cancer, the median duration of patient delay ranged from 56 to 75 days (38-40). The median duration of patient delay was longer in glottic cancer than in supraglottic cancer, but the significance of this difference is inconsistent across studies (38,41). For professional delay, the median length reported for laryngeal cancer was between 25 to 84 days (38-40). Patients with glottic cancer were also significantly more likely to experience professional delay longer than 30 days compared to supraglottic cancer patients (40). Researchers have hypothesized that the extended patient and professional delays observed in glottic cancer can be attributed to the nature of the symptoms and stage at which symptoms present. As described previously, hoarseness appears in the early stages of glottic cancer, but the harmless nature of this symptom may cause patients to delay seeking help. In comparison, symptoms of supraglottic cancer do not present until the disease is more advanced, but the combination of symptoms is more alarming and patients will likely contact a health care provider more immediately (41). Additionally, since patients with glottic cancer seek help in the early stages of disease, the small tumours are difficult to detect and diagnose, resulting in increased professional delay (39).

The rationale for studying diagnostic delay and stage at diagnosis in head and neck cancers is that a longer duration between the onset of symptoms to diagnosis will lead to advanced-stage cancer, as a result of tumour growth over time (36). Eight studies that examined the association between diagnostic delay and stage at diagnosis in laryngeal cancer were identified. Studies by Allison et al. (25) and Teppo et al. (42) reported that neither patient nor professional delay were associated to advanced-stage laryngeal cancer. Raitiola and Pukander (19) found that total diagnostic delay was significantly longer in advanced-

stage laryngeal cancer compared to early-stage disease. However, this association was not significant when stratified by laryngeal cancer subsite (19). Similarly, three studies that analysed glottic and supraglottic subsites separately found that the neither total, patient, nor professional diagnostic delay were significantly related with stage at diagnosis (36,38,41,43). When laryngeal cancer was studied in conjunction with hypopharyngeal cancer, Amir et al. (44) reported no relationship between patient delay and stage at diagnosis. However, another study of these two head and neck cancer sites identified a positive association between patient delay and stage at diagnosis, but the statistical significance of this finding was marginal (5). Evidence for the relationship between diagnostic delay and stage at diagnosis in laryngeal cancer is inconclusive and varies according to the cancer sites that are studied. This suggests that tumour biology and histology may be more important determinants of cancer stage than diagnostic delays.

2.4.5 Health Care Utilization Prior to Diagnosis and Stage at Diagnosis

As indicated in Andersen's Behavioural Model for Health Care Use, utilization of health services is an important determinant of health outcomes. Research examining health care utilization prior to the diagnosis and stage at diagnosis has been related to identifying whether opportunities to improve early diagnosis of head and neck cancers exist through a patient's usual health care. However, few studies to date have investigated this relationship. In a study by Prout et al. (45), the median number of health care visits in the 24-months preceding diagnosis was significantly lower for patients with advanced-stage head and neck cancer versus those with early-stage disease (i.e. T1N0). Similarly, a study among patients with head and neck cancer found that, in comparison to those requiring regular follow-up for multiple morbidities, a significantly greater proportion of patients with no medical conditions were diagnosed with T3 or T4 cancer (29). A recent population-based study from the United

States also examined health care encounters in the year prior to diagnosis among a cohort of head and neck cancer patients aged 65 years or older (8,26). Using SEER and Medicare data, Reid et al. (8) found that, among patients with laryngeal cancer, having six or more pre-diagnostic physician visits in a one-year period was strongly associated with a reduced odds of regional or distant disease at diagnosis compared to having no physician visits before diagnosis. This association was seen for patients without known alcohol- and tobacco-related co-morbidities and was strengthened for patients with one or more known co-morbidities (8).

In this population-based study, Reid and Rozier (26) also reported that having high continuity of care with the same internist was associated with local disease at diagnosis for head and neck cancers, but the effect was relatively weak. On the other hand, having continuous care with a general or family physician did not exhibit the same relationship (26). The association between continuity of care and stage at diagnosis was also dependent on the site of cancer. For laryngeal cancer, there was a 16% reduction in the odds of advanced-stage disease for patients with high continuity compared to those with low continuity, but the statistical significance was marginal (26). Based on evidence to date, it appears that the frequency of health care encounters prior to diagnosis is negatively associated with stage, while there is also a negative relationship between continuity of care and stage at diagnosis.

2.5 Health Care Utilization

Research examining health care utilization among laryngeal cancer patients is limited. However, understanding a person's use of health services has important implications for health policy and practice. Utilization can be measured using health administrative data, data from chart abstractions, as well as self-reported data (46). Although standard measures of health care utilization have not been defined, measures of utilization generally focus on the amount of health care use and the type of health service (47). These measures correspond

with the key characteristics of health care utilization proposed by Andersen and Newman, which are the type of health service (i.e. physician, hospital, or drug) and the purpose of care (i.e. prevention, diagnosis, or treatment) (48). Additionally, Andersen and Newman state that an important characteristic of health care utilization is the unit of measurement (i.e. number of services, initial contact, or episodes of care), which is dependent on the purpose of the research (48). Therefore, all three elements of health care utilization should be considered.

2.5.1 Frequency of Health Care Use

The frequency of health care visits is frequently used to measure the volume of health care utilization. In the 2002-2003 fiscal year, the average number of office visits to a general physician or family physician (GP/FP) by Ontarians aged 40 years and older ranged from four to nine. For patients who were treated by both a GP/FP and specialists, the number of visits per person was between nine and seventeen (49). For both men and women, the average number of visits per year increased with age and the rate of visits did not vary significantly by sex among older adults (49). The types of physicians seen also changed with age, where a greater proportion of older patients were treated by both GP/FPs and specialists (49). Overall, children under the age of five years and the elderly had the highest rates of emergency department use in Ontario (50). A study of Ontario residents aged 65 years and older reported the average number of emergency department visits to be 0.6 visits in a year, which is more than two times greater than the average number of visits for the population of Ontario (50,51).

Frequency of health care utilization has been examined as predictor of cancer outcomes. As described previously, two studies found a negative association between the frequency of health care visits and the stage of diagnosis in laryngeal cancer (8,45). This association has also been studied for breast cancer and colorectal cancer. Keating et al. (52)

examined all office visits to a primary care provider, medical specialist, or other specialists two years before diagnosis among breast cancer patients aged 65 years and older. This study found that women with more pre-diagnostic health care visits were less likely to be diagnosed with advanced-stage breast cancer. Interestingly, adjustment for mammography use reduced the effect of the frequency of health care visits on stage at diagnosis, suggesting that breast cancer screening is a partial mediator of the association (52). In the study of colorectal cancer patients, the number of primary care provider visits and non-primary care provider visits two years before diagnosis were independently associated with stage at diagnosis (53). Ferrante et al. (53) found that, compared to patients with zero or one visit, patients who saw a primary care provider 11 or more times were 1.41 times more likely to have early-stage disease, while patients who saw a non-primary care provider 11 or more times were 1.61 times more likely to have early-stage disease. Colorectal cancer screening, however, did not explain the association observed between health care utilization and stage at diagnosis (53).

2.5.2 Continuity of Care

Continuity of care describes the extent of coherence, consistency, and connectedness in a patient's health care (54). One component of continuity of care is the on-going relationship between the patient and their health care providers, which is known as relational or interpersonal continuity (54,55). In Ontario, adults aged 40 years and older experienced high continuity of care with their GP/FP. More specifically, these patients had between 80% and 90% of their GP/FP visits with the same physician (56). However, it is important to note that continuity of care could not be assessed for 30% of adults aged 20 years and older because these individuals had less than three visits with a GP/FP in the two-year period (56).

Continuity of care is an important measure of health care utilization for describing a patient's care. Reviews of the literature have reported that continuity of care is consistently

associated with improved health outcomes. A systematic review by van Walraven et al. (57) found that eight out of the nine studies reviewed reported a strong association between increased relational continuity and decreased hospitalization, emergency department visits, or length of stay, while the ninth study found a marginal association. Similarly, the review by Saultz et al. (55) concluded that good interpersonal continuity was associated with lower rates of hospitalization. There is also evidence showing a positive association between relational continuity and patient satisfaction with the care received (57). Furthermore, studies have shown that patients who had higher continuity of care were more likely to have preventive care, including vaccination and cancer screening (55).

2.5.3 Use of Preventive Services

Research on health care utilization has also examined use of preventive services. Use of preventive health care can help reduce morbidity and mortality (58). This measure of utilization is important because it provides an indication of the quality of primary health care, as well as an individual's health behaviours (23,59). The Canadian Task Force on Preventive Health Care recommends a number of preventive services for adults. These include mammography for women aged 50 to 69 years (60); Papanicolaou (Pap) test for women aged 18 to 69 years (or following the initiation of sexual activity) (61); fecal occult blood test, sigmoidoscopy, or colonoscopy for men and women aged 50 year or older with average colorectal cancer risk (62); and annual influenza vaccination for healthy adults (63).

Overall, the uptake of cancer screening in Ontario has improved over the last decade. Since the 2002-2003 period, the proportion of women aged 50 to 69 years that had a mammogram increased by 7%, with 66% of eligible women receiving breast cancer screening in 2008-2009. Similarly, for women aged 40 to 69 years, there was a significant increase in cervical cancer screening participation between the 2001-2003 period and the

2007-2009 period (64). Within this age group, the proportion that received a Pap test in 2007-2009 ranged from 68% to 73%, decreasing with age (65). For colorectal cancer screening, the proportion of men and women that received a fecal occult blood test increased significantly from 13% to 30% between 2002-2003 and 2008-2009 (66). Estimating the uptake of influenza vaccination is more difficult because the vaccine can be administered in a variety of settings, such as doctor's offices, public health units, schools, and community centres. Using self-reported vaccination status and administrative data, the proportion of Ontarians aged 12 and up that received the influenza shot in 2000-2001 was 37%. Older adults were more likely to be vaccinated, where 47% and 75% of adults aged 50-64 years and 65 years and up, respectively, had the influenza vaccine (67).

Use of preventive services is an important factor to consider when investigating variations in cancer stage at diagnosis. Gornick et al. (59) hypothesized that individuals who used more preventive services would be less likely to be diagnosed with late stage cancer. This hypothesis was drawn from the ideas that preventive services use is correlated with other health behaviours and it encourages communication with health care providers about any signs and symptoms (59). Gornick et al. (59) examined whether use of preventive services (influenza and pneumonia immunization; breast, cervical, colon, and prostate cancer screening) was associated with stage of cancer diagnosis. This study found a negative association between the proportion of patients with advanced-stage cancer and the number of preventive services used. Use of two or more preventive services was associated with stage at diagnosis for uterine and male bladder cancers (59).

2.6 Summary

Most of the studies investigating variations in stage at diagnosis of laryngeal cancer have been conducted in populations in the United States or Europe. An important limitation

of this research is that the findings may not be applicable to laryngeal cancer patients in Canada due to differences in health care systems and cultures. Research examining the effect of health care utilization on stage of laryngeal cancer, in particular, is insufficient and needs to be examined in Canadian populations. Previous studies on pre-diagnostic health care utilization among laryngeal cancer patients have not examined the subsites individually due to inclusion with other head and neck cancers and relatively small sample sizes. However, glottic cancer and supraglottic cancer have distinct disease characteristics and symptom profiles, so the overall relationships observed for head and neck or laryngeal cancers may not be true for the individual disease sites. In addition, not all of the studies have accounted for demographic and clinical characteristics that have been shown to be associated with health care use and stage at diagnosis. Furthermore, studies on health care utilization prior to diagnosis of laryngeal cancer have failed to distinguish health care encounters attributed to the cancer from usual patterns of health care use. It is necessary to study these periods of utilization separately because they address different patient and system characteristics that contribute to an advanced diagnosis of laryngeal cancer. Therefore, understanding usual pre-diagnostic health care use among laryngeal cancer patients and its relationship to stage at diagnosis in the Canadian context is essential to help improve early detection and diagnosis of laryngeal cancer and subsequent outcomes.

CHAPTER 3 METHODS

3.1 Study Objectives and Hypotheses

The aim of the current study was to understand patterns of usual health care utilization among laryngeal cancer patients. Specifically, the study objectives were:

1. To compare patterns of usual health care utilization between a cohort of laryngeal cancer patients and a matched cohort of the general population in Ontario and to determine if persons who are diagnosed with laryngeal cancer use the health care system differently than those who do not get laryngeal cancer.

   Hypothesis: The frequency and continuity of health care encounters among laryngeal cancer patients was hypothesized to be lower than the general population. It was also hypothesized that enrolment in primary care models would be similar between the two populations. However, in comparison to the general population, laryngeal cancer patients were expected to be less likely to use preventive services.

2. To examine the associations between usual health care utilization prior to the diagnosis of laryngeal cancer and stage at diagnosis in a cohort of patients in Ontario.

   Hypothesis: Laryngeal cancer patients with low frequency and continuity of health care encounters were hypothesized to be more likely to be diagnosed with advanced-stage disease. Also, patients who were not enrolled in primary care model were expected to have advanced diagnoses. Furthermore, it was hypothesized that patients with little or no use of preventive services would have a higher likelihood of advanced laryngeal cancer at diagnosis.

3.2 Study Design

The current study linked existing clinical, demographic, and health administrative data from the Institute for Clinical Evaluative Sciences (ICES) data holdings and the Division of Cancer Care and Epidemiology (CCE) Cancer Care Database. Using these data, information on subjects' health care encounters during a two-year period prior to their study index date was collected to measure usual health care utilization. Specifically, usual health care use was characterized according to the frequency, types, and continuity of care. For Objective 1, a case-control study design was used to contextualize usual health care utilization among laryngeal cancer patients in comparison to the general population. A retrospective cohort study design was used to address Objective 2, which was the main objective of the study. This design allowed the relationship between usual health care use and stage of laryngeal cancer at diagnosis to be examined.

The candidate was responsible for the design of the study, preparing the dataset creation plan, and conducting the statistical analyses. The dataset creation plan defined the data sources, relevant data elements, and specific data values needed to derive variables for the study (see Appendix A). Using the dataset creation plan, Ms. Marlo Whitehead, who is a senior analyst at ICES@Queen's, performed the data linkages and processed the data to create the study dataset with the requested variables. Subsequent data processing to derive final study variables was performed by the candidate.

3.3 Data Sources and Linkage

Data for the current study were obtained from the following ten data sources: (1) the Ontario Cancer Registry, (2) the Division of Cancer Care and Epidemiology stage file, (3) the Ontario Health Insurance Plan claims database, (4) the Canadian Institute for Health Information Discharge Abstract Database, (5) the Client Agency Program Enrolment

database, (6) the Ontario Breast Screening Program database, (7) the Institute for Clinical Evaluative Sciences Physicians Database, (8) the Registered Persons Database, (9) PSTLYEAR files, and (10) PCCF files. As shown in Figure 3-1, these databases contain cancer system data, health services data, data on health care providers, as well as population and demographic data. The Ontario Cancer Registry (OCR) and the CCE Stage File are part of the CCE Cancer Care Database, located at the Queen's Cancer Research Institute. The remaining databases, as well as the OCR, are part of the ICES data holdings. The data sources that contributed to the study dataset are described in further detail.

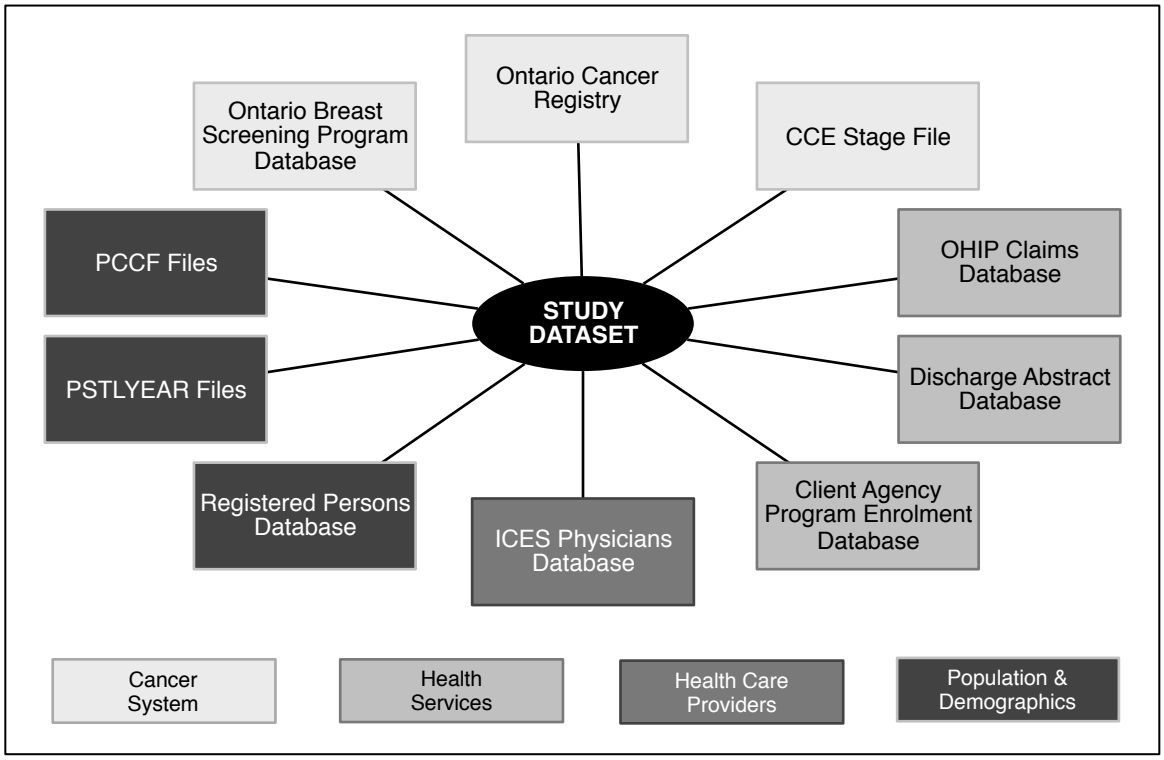

Figure 3-1. Data sources contributing to the study dataset.

3.3.1 Ontario Cancer Registry

The Ontario Cancer Registry (OCR) is a population-based registry that captures information on all incident cases of cancer in Ontario (68,69). The OCR is maintained by Cancer Care Ontario (CCO) and is estimated to capture over 95% of cancer cases for all sites

(33,69). This registry is based on a passive reporting system and is created by linking records from four sources: Canadian Institute for Health Information (CIHI) hospitalization data, cancer centre patient records, pathology reports, and death certificates (68,69). The OCR contains information on patient demographics, date of diagnosis, primary cancer site using the International Classification of Diseases, 9th or 10th Edition (ICD-9 or ICD-10), and the histologic diagnosis according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3).

The date of diagnosis recorded in the OCR is based on the earliest diagnosis of cancer appearing in cancer centre records or hospitalization data (70). A computerized case resolution system is used to assign primary cancer site if there are discrepancies among the data sources. This system primarily considers the specificity of the recorded site and the reliability of the data source (69). A recent study assessed the quality of these data elements for head and neck cancers by comparing the OCR data to clinical data collected at a cancer centre. Hall et al. (70) found that the date of diagnosis, within one month, was concordant for 91% of the cases. Regarding cancer site, the study reported that the OCR captured 81% of all head and neck cancers, while the accuracy rate for site assignment was 91% for all cancers of the head and neck. The highest detection (90%) and accuracy (97%) rates were reported for laryngeal cancer (70).

3.3.2 Division of Cancer Care and Epidemiology Stage File

The CCE stage file was originally created to examine the distributions of stage at diagnosis by socio-demographic characteristics for various cancer sites (33). This dataset was assembled at the Division of Cancer Care and Epidemiology using data files provided by Cancer Care Ontario. The patient identifier and disease number were used to link the Oncology Patient Information System stage and disease files, in order to compile

comprehensive information for cancer cases treated at Ontario's Regional Cancer Centres (RCC). A subsequent data linkage to the RCC source file, based on the disease site and registration date, was necessary to remove patients who were not residents of Ontario (71). Approximately 98% of laryngeal cancer patients receive their primary treatment at one of the province's cancer centres (15) and were captured in this database.

The CCE stage file contains the OCR unique identifier, demographic information, and administrative data, such as the RCC registration date and referral dates. The main information in the dataset is clinical data related to the cancer. These data include, the ICD-9 diagnostic codes, the ICD-O-3 histology codes, and the date of diagnosis. For stage at diagnosis, the variables that are available include clinical and pathological tumour, node, and metastasis (TNM) stage, as documented by the clinician. Variables for clinical and pathological stage groups, as reported by the physician, are also available in the CCE Stage File (33,71). Cancer Care Ontario reported that approximately 90% of laryngeal cancer cases diagnosed in 2007 had valid stage group recorded, compared to a 70% stage capture rate for all cancers that have a TNM stage classification (72).

3.3.3 Ontario Health Insurance Plan Claims Database

The Ontario Health Insurance Plan (OHIP) claims database contains data for all claims made by health care providers who provide services covered under the OHIP. Each record represents one service provided by a health care provider to a patient. The data elements included for each record are patient identifiers, date of service, fee codes for the type of service, diagnosis codes, physician identifiers for treating and referring physicians where applicable, and physician specialty (73,74). The OHIP database includes both fee-for-service billings and shadow billings. Approximately 5% of physicians in Ontario are remunerated under an alternate funding plan (AFP) and submit shadow billings to replicate

fee-for-service billings (73). However, shadow billings do not capture all of the services provided by these physicians because physicians who work in Community Health Centres or Family Health Organizations (formerly known Health Service Organizations (75)) are not required to submit shadow billings. Particular attention must be given to the South East, North East, Waterloo Wellington, and Hamilton Niagara Haldimand Brant Local Health Integration Networks (LHINs) because they contain large Community Health Centres or Family Health Organizations (73), so physician services in these regions may be underrepresented in the OHIP claims database.

3.3.4 Canadian Institute for Health Information Discharge Abstract Database

The CIHI Discharge Abstract Database (CIHI-DAD) contains data from hospital discharge records including patient demographics, administrative data for admissions and discharges, and clinical data for diagnoses and procedures (76). Using standard data abstraction forms, information is collected from patient charts to prepare a discharge abstract (77). All hospital discharges in Ontario, including acute care, chronic care, rehabilitation, and same-day surgeries, are captured in the CIHI-DAD (76). An Ontario study that compared data from the 2002-2003 CIHI-DAD to re-abstracted chart data found that there was 99.9% agreement for admission and discharge date variables, while there was 95% agreement for variables characterizing patient transfers (78). A similar data re-abstraction study for the 2005-2006 CIHI-DAD reported the sensitivity and reliability of diagnosis codes to be 75% and 72%, respectively, in Ontario (76,78). Thus, non-clinical data recorded in the CIHI-DAD is highly reliable, but diagnoses may be underreported in this database.

3.3.5 Client Agency Program Enrolment Database

The Client Agency Program Enrolment (CAPE) database is created by ICES using regularly provided data from the Ministry of Health and Long-Term Care (MOHLTC). The

database consists of records for all individuals who are enrolled in a primary care model, such as Family Health Networks, Family Health Groups, and Family Health Organizations. The database captures information on the patient's date of enrolment, end of enrolment, type of model, and the affiliated physician's billing number. Based on an internal evaluation, the number of individuals enrolled in a primary care model recorded in the CAPE database is comparable to those reported by the MOHLTC (79).

3.3.6 Ontario Breast Screening Program Database

Data in the Ontario Breast Screening Program (OBSP) database are provided by Cancer Care Ontario. The OBSP database contains information for women who are enrolled in Ontario's organized breast cancer screening program (80,81). The main data included in this database relate to the client (i.e. eligibility, recruitment, clinical data), screening, and breast cancer diagnosis. With regards to screening, information is recorded on the type of screening performed, which include mammography and physical examination (80).

3.3.7 Institute for Clinical Evaluative Sciences Physicians Database

The ICES Physicians Database (IPDB) is assembled and maintained by ICES. This database combines information from the Corporate Provider Database, the Ontario Physician Human Resource Data Centre (OPHDRC) database, and the OHIP claims database. The OPHRDC verifies its data by conducting telephone interviews with physicians. These data are used to validate the information in the Corporate Provider Database during the creation of the IPDB. The IPDB includes data on physician demographics, physician speciality, training and certification, and services provided (74,81).

3.3.8 Registered Persons Database

The RPDB is a population-based registry that is maintained by the Ministry of Health and Long-Term Care. The data received at ICES is stripped of all personal identifiers and

replaced with an encrypted, unique identifier, which is known as the ICES key number. This database contains records for all individuals who have been issued an Ontario health card number. The RPDB includes basic demographic data, such as date of birth, sex, postal code, and date of death if applicable. In addition, the RPDB documents any changes in eligibility for coverage under the OHIP (74,81).

3.3.9 PSTLYEAR Files

The PSTLYEAR files are assembled using multiple data sources at ICES and contain records for all individuals in the RPDB. Individual PSTLYEAR files have been created for each year, beginning in 1991. The main element in this database is the most accurate postal code known for an individual on July 1st of a given year. The postal code is determined from various data sources at ICES, including the RPDB and CIHI-DAD. The PSTLYEAR file also contains other important geographic variables. These variables include LHIN, census subdivision, and dissemination area, which are based on the documented postal code (82).

3.3.10 PCCF Files

The PCCF files housed at ICES are derived from Statistics Canada Postal Code Conversion Files. There are separate PCCF files corresponding to each census year, including the 2001 PCCF file and 2006 PCCF file used in the current study. The main purpose of the PCCF file is to link postal codes with identifiers for various geographic areas used in census data. Geographic areas include dissemination area, census subdivision, and census metropolitan area or agglomeration. A number of area-level measures derived from census data are also contained in this file, such as neighbourhood income quintile, urban or rural indicators, and population size (83,84).

3.3.11 Data Linkage

To create the study dataset, an initial cohort of laryngeal cancer patients was identified using data in the CCE Cancer Care Database. In accordance with the agreed protocol for transferring data from the CCE to ICES, these cancer data were transferred to Cancer Care Ontario via a dedicated, secure virtual private network. After staging data were updated at CCO, encrypted data were transferred to ICES where a unique identifier (i.e. ICES key number) was added to the cancer data. The ICES key number enabled the cancer data to be linked with the other databases at the Institute for Clinical Evaluative Sciences. Two exceptions were data from the ICES Physicians Database and the PCCF files, which were linked by service provider number and geographic region, respectively.

3.4 Study Population

In the case-control study for Objective 1, the study population consisted of subjects in the laryngeal cancer cohort and the comparison cohort. These two cohorts were defined as the case and control groups, respectively. The study population for Objective 2 included patients in the laryngeal cancer cohort only.

3.4.1 Laryngeal Cancer Cohort

The target population for the laryngeal cancer cohort included all patients in Ontario, age 40 years or older, who were diagnosed with single, primary, squamous cell carcinoma of the glottis or supraglottis (ICD-9 codes: 161.0 and 161.1; histology codes: 8050, 8052 to 8084) between January 1, 2002 and December 31, 2008, were treated at a Regional Cancer Centre, and had a valid ICES key number. This time period was chosen based on staging data availability. A total of 2,062 laryngeal cancer patients were identified following the linkage of data from the CCE Cancer Care Database to data from ICES data sources. Of the patients who met the inclusion criteria, individuals were excluded if they did not have

Ontario Health Insurance Plan coverage during the three years before diagnosis or sufficient information to determine stage grouping. Patients were subsequently excluded because five matched-controls could not be identified. Therefore, the study population for the laryngeal cancer cohort consisted of 1,702 patients (see Figure 3-2). For these patients, the study index date was defined as the date of laryngeal cancer diagnosis.

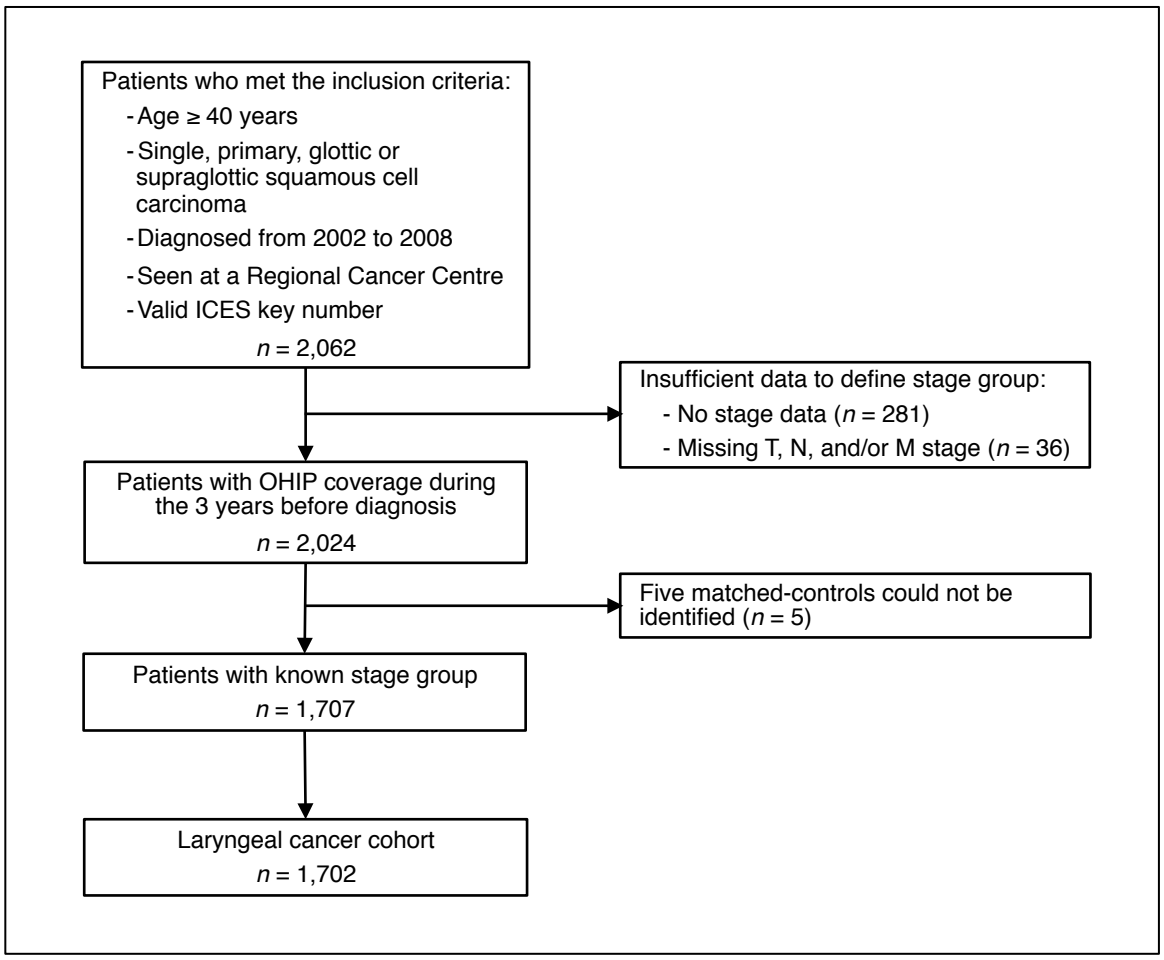

Figure 3-2. Definition and size of the laryngeal cancer cohort.

3.4.2 Comparison Cohort

The comparison cohort was comprised of population-based controls identified from the RPDB. The control group was a random sample of Ontario residents who had a valid ICES key number and did not have a previous diagnosis of cancer. Individual matching within five years of the birth year, by sex, and by geographic area was utilized to select

controls. The geographic unit that was used for matching was secondary sub-divisions of LHINs (subLHINs). These are smaller areas defined by each LHIN for the purposes of planning health services and there are 141 secondary subLHINs in Ontario (85). Controls were assigned a study index date that corresponded with the date of diagnosis of the matched laryngeal cancer patient. Only individuals who were covered by the OHIP in the three years preceding the study index date were included in the control group. Five controls were selected per laryngeal cancer patient, resulting in a total of 8,510 subjects in the comparison cohort.

3.5 Study Period

Previous research examining the use of health services before the diagnosis of head and neck cancer found that there was a significant increase in the number of health care encounters in the three months directly prior to diagnosis (45). Since the increase in health care use during this time interval may be attributed to cancer symptoms and the current study was interested in usual patterns of health care use, the three months preceding the study index date were excluded from the study period. Thus, the study period for usual health care utilization was defined as the time between the 3rd and 27th month before the study index date (see Figure 3-3). A 24-month study period allowed for more stable estimates of usual health care utilization. Additionally, a two-year look back period allowed for the use of annual preventive services to be captured, but the look back period was extended to measure the use of those preventive services that have longer recommended intervals.

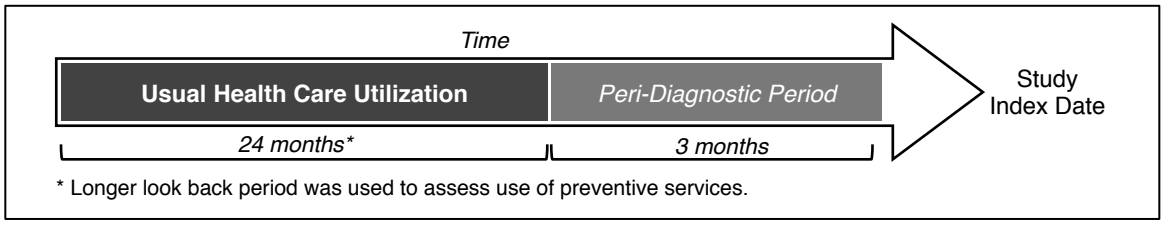

Figure 3-3. Study period for usual health care utilization.

3.6 Study Variables

Figure 3-4 presents the conceptual models for Objective 1 and Objective 2 of the current study. The exposure of interest in the study was usual health care utilization, which was characterized using four different measures. The outcome variables in the study were disease status for Objective 1 and disease stage at diagnosis for Objective 2. Several demographic and health-related characteristics were also considered as potential confounders or effect modifiers in the analyses. Detailed definitions of the study variables, specifying data elements and values, were part of the dataset creation plan (see Appendix A). This document informed the analyst at ICES@Queen's on how to process the data and create the study dataset.

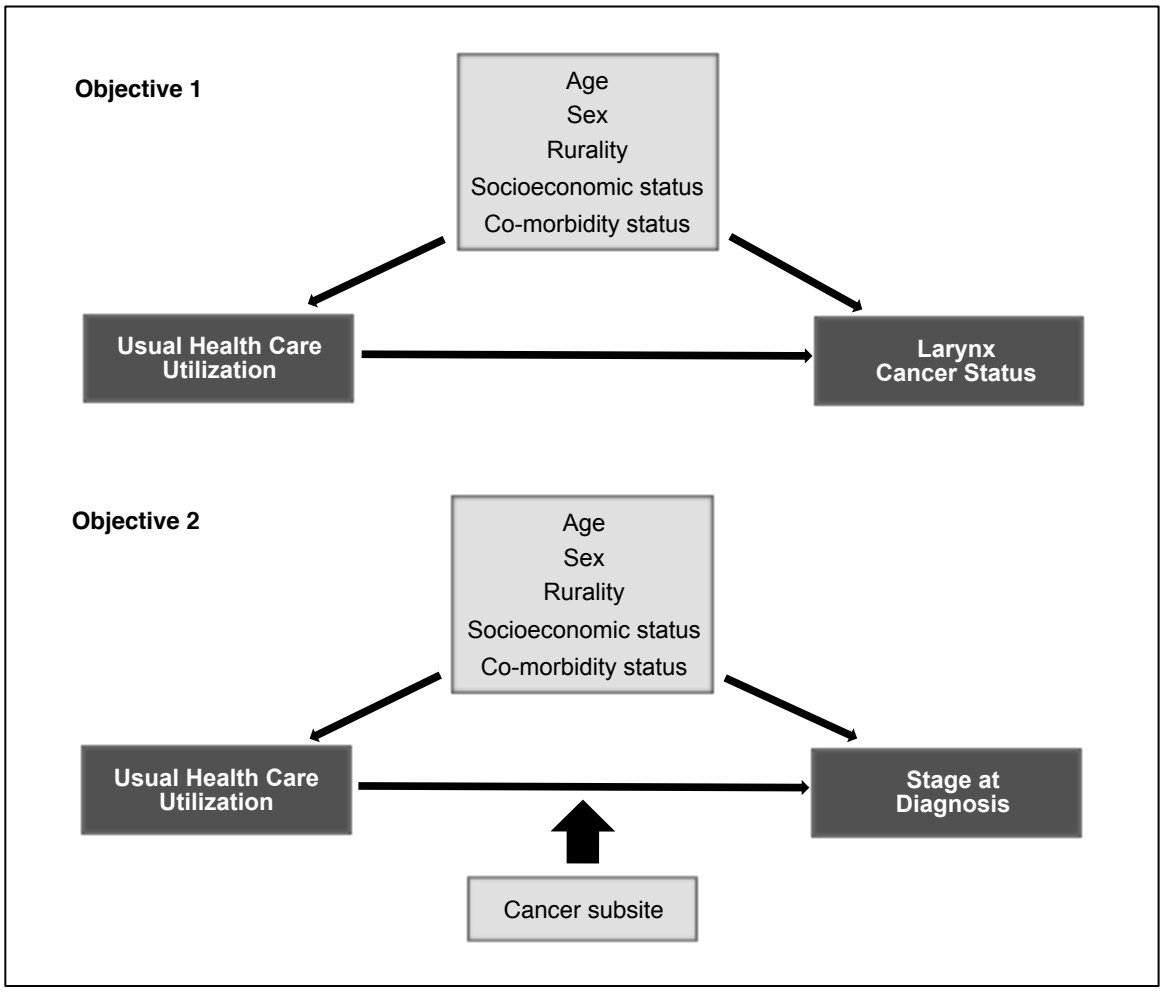

Figure 3-4. Conceptual models for Objective 1 and Objective 2 of the study.

3.7 Usual Health Care Utilization

Usual health care utilization was characterized by the frequency, continuity, and types of health care. The specific types of care that were of interest in the current study were enrolment in a primary care model and use of preventive health services. These types of care were chosen because they may provide an indication of patient health-seeking behaviours. Usual health care utilization variables were derived using relevant data elements from various databases.

3.7.1 Frequency of Health Care Encounters

The frequency of health care encounters was defined as the total number of office-based visits, emergency department visits, and hospital admissions for an individual during the two-year study period. Data were extracted from the OHIP claims database and the CIHI-DAD to obtain this measure of usual health care utilization.

To identify office-based visits and emergency department visits in the OHIP claims database, the location of physician services was determined by implementing an ICES macro that utilizes an algorithm based on OHIP fee codes (86). Only physician consultations and visits from the OHIP fee schedule were considered. Office-based encounters included visits in physician offices, home-visits, phone consultations, visits in long-term care facilities, as well as visits where the location could not be defined. For the current study, only emergency department visits in which the patient was assessed by a physician were captured (50). For each study subject, OHIP claims submitted by the same physician for the same day were counted as a single encounter to prevent overestimation of ambulatory visits. Following this rationale, hospital admissions were identified using the episode of care variable in the CIHI-DAD. The definition of an episode of care is a series of hospital admissions linked by patient transfers. Therefore, using this variable for hospitalizations eliminated duplicate discharge

records, as well as records where admission and discharge dates overlapped (87). The choice between use of a continuous versus categorical representation of the frequency of health care encounters was made by assessing the linearity assumption in regression analyses (88).

3.7.2 Continuity of Care

Another measure of usual health care utilization that was considered in the study was continuity of care. Specifically, relational continuity between a patient and their general practitioner or family physician (GP/FP) was assessed using the Usual Provider Continuity (UPC) index (54,89). The UPC index represents the proportion of visits attributed to the health care provider seen most frequently. While this measure is easily derived from health administrative data and widely used in primary care research, estimates are unreliable for low-users of health care (54,89). Therefore, the UPC index was only calculated for individuals who had three or more office-based visits with their family physician during the 24-month study period (56). Health care visits were extracted from the OHIP claims database and included specialist visits, which were attributed to the referring GP/FP (56). GP/FPs were identified from the IPDB using the physician number and included physicians whose specialities were documented as GP/FP, FP/emergency medicine, emergency medicine, or community medicine. High continuity of care was defined as a UPC index of 0.75 or greater (56).

3.7.3 Primary Care Model Enrolment

Primary care models were implemented in Ontario beginning in the late 1990's. The aim of these models was to improve access to primary health care services and provide comprehensive care. A number of primary care models currently exist in Ontario, including the Comprehensive Care Model, Family Health Group, Family Health Network, Family Health Organization, Family Health Team, and Community Health Centres (75). Primary

care models include requirements for physicians to provide after-hours care and on-call service for the Telephone Health Advisory Service. In addition, these models offer incentives for providing specific care to enrolled patients including, preventive care management (i.e. cancer screening and vaccinations), smoking cessation counselling, and diabetes management (75,90). A patient is enrolled into a physician's practice by signing an enrolment and consent form (75). For the current study, individuals were classified as being enrolled in a primary care model if the CAPE database record indicated that enrolment was before the study period and enrolment was not terminated. Individuals who did not have a record in the CAPE database or ended enrolment prior to the study period were classified as not being enrolled in a primary care model.

3.7.4 Use of Preventive Services

Five preventive services considered in the current study were: physical examination, influenza vaccination, colorectal cancer screening, breast cancer screening, and cervical cancer screening. As discussed previously, the study period was extended to examine use of preventive services. This applied specifically to cancer screening because the recommended schedules were longer than the two-year study period. Thus, the study period for assessing each preventive service was the length of the recommended screening interval plus a one-year buffer period, to ensure that use of preventive health care was captured. Dichotomous measures (i.e. yes or no) were created to evaluate the use of each preventive service. A summary preventive services index was also created to measure an individual's adherence to recommendations for preventive health care (see Section 3.7.4.2).

3.7.4.1 Preventive Services

Annual physical examination status and influenza vaccination status during the two-year study period were assessed for the entire study population using the OHIP claims

database. Physical examinations were identified using the OHIP fee code and corresponding diagnostic code for an annual health exam (91). As described by Kwong et al. (67), influenza vaccinations were captured using the influenza vaccination OHIP fee codes plus OHIP fee codes occurring for general vaccination in October or November. This algorithm of OHIP fee codes had 56% sensitivity and 97% specificity, in comparison to self-reported influenza vaccination status in the Canadian Community Health Survey (67).

Colorectal, breast, and cervical cancer screening status were only assessed for individuals who were eligible to receive the service for a minimum of one year. Eligibility was determined by the age criteria of Ontario's cancer screening programs. The algorithms used to identify the procedures were based on the definitions from previous research utilizing ICES data (56,81,92,93). However, these algorithms capture examinations conducted for screening and diagnostic purposes. This is because it is not always possible to establish the reason for the procedures using only health administrative data (56,94). Thus, for the purposes of this research, the colorectal, breast, and cervical examinations conducted for cancer screening or symptom assessment were considered preventive services.

Based on the algorithm by Jaakkimainen et al. (56), OHIP fee codes were used to determine if male and female subjects aged 50 to 74 years had any of the following colorectal investigations for screening or diagnostic purposes: fecal occult blood test (3-year period), rigid or flexible sigmoidoscopy (6-year period), single or double contrast barium enema (6-year period), or colonoscopy (11-year period) (56,95,96). Among the eligible study controls (i.e. comparison cohort), 64% of those who had a colorectal examination during the study period only received one test.

The use of mammography for breast cancer screening or diagnostic assessment was ascertained for females between the ages of 50 and 69 years during a four-year period. This was assessed using the fee codes for mammography in the OHIP claims database or data on

the types of screening recorded in the OBSP database (92,97). Both data sources were necessary to assess mammography because mammograms received through the OBSP are covered by global funding and are not captured in the OHIP claims database (98). Of the eligible females in the current study's comparison cohort who received a mammogram, 73% had one mammogram in the study period.

Females aged 40 to 69 years, without a previous hysterectomy, were assessed to determine whether a Pap test was received to screen for cervical cancer or assess signs and symptoms (56,99). An algorithm of OHIP fee codes for procedures and laboratory tests, which has been used by Lofters et al. (93), was used to determine Pap test status within a four-year period. This algorithm has been validated against Cytobase, which is Ontario's electronic Pap test registry, and demonstrated 99.5% sensitivity and 85.7% specificity (93). Thirty-six percent of the eligible female controls who had a Pap test received one test during the study period.

3.7.4.2 Preventive Services Index

Eligibility for preventive services depends on sex and age (see Table 3-1). In order to evaluate the use of preventive services for the entire study population, a preventive services index was created to measure a person's overall propensity for using preventive health care. The preventive services index scores were calculated as the proportion of preventive services used, out of the total number of preventive services for which an individual was eligible. Therefore, the preventive services index captures the concept of being up-to-date for preventive health care (100,101). Scores from the preventive services index were subsequently categorized into four groups: no preventive services, > 0% and ≤ 50% of eligible preventive services, > 50% and < 100% of eligible preventive, and up-to-date for preventive services (i.e. 100%).

Table 3-1. Eligibility criteria for preventive services by sex and age.

	Males (age, years)				Females (age, years)			
Preventive Service	**40–49**	**50–69**	**70–74**	**≥ 75**	**40–49**	**50–69**	**70–74**	**≥ 75**
Physical examination	X	X	X	X	X	X	X	X
Influenza vaccination	X	X	X	X	X	X	X	X
Colorectal cancer screening		X	X			X	X	
Breast cancer screening						X		
Cervical cancer screening						X		

3.8 Stage at Diagnosis

Stage at diagnosis was defined using tumour-node-metastasis (TNM) classification, which is the classification system adopted by the International Union Against Cancer and the American Joint Committee on Cancer (21,102). Specifically, the current study classified stage at diagnosis using stage groups (Stage I, II, III, and IV), as well as a broader classification of early-stage (Stage I or II) and advanced-stage (Stage III or IV) disease. The dichotomous categorization of stage at diagnosis was selected because of its significance for clinical practice. Additionally, this classification is frequently used in cancer research, including studies that have examined predictors of stage (5,24,25).

Staging data was obtained from the CCE stage file. The stage group was derived from the individual tumour, node, and metastasis classifications. Patients with a missing M classification were assumed to have M0 because metastatic investigations are not always performed for early-stage disease. The physician-recorded stage group was used when stage group could not be determined because tumour or node information was missing. Stage at diagnosis was assigned using both clinical and pathological stage groups in order to increase the number of laryngeal cancer patients included in the study. Clinical stage group was the primary method of classification because it was more commonly available than pathologic stage. Table 3-2 shows the distribution of the methods used to determine stage at diagnosis for the laryngeal cancer cohort.

Table 3-2. Classification methods used to assign stage at diagnosis of laryngeal cancer.

Classification Methods	Laryngeal Cancer Cohort (*n* = 1,702)
1. Clinical TNM-derived stage group	92.54%
2. Clinical physician-recorded stage group	2.64%
3. Pathological TNM-derived stage group	4.47%
4. Pathological physician-derived stage group	0.35%

3.9 Covariates

A number of covariates were considered to ensure that confounding did not bias the associations of interest. Specifically, these variables were selected based their relationship with stage at diagnosis of laryngeal cancer and usual health care utilization, which were the outcome and the exposure for the main objective, respectively. Table 3-3 lists the covariates and a brief rationale for their inclusion in the study.

Table 3-3. Summary of rationale for examining the covariates in the study.

Covariate	Rationale
Age	Younger age at diagnosis is associated with late-stage laryngeal cancer (24-26). Additionally, older adults are more likely to have visited a doctor, but less likely to have seen a specialist than younger adults (23,103).
Sex	Females are more likely to have advanced-stage laryngeal cancer at diagnosis (24). Females are also more likely than males to use health care, including having influenza vaccinations, visiting a physician, being hospitalized, and having a regular doctor (23,103).
Rurality	The effect of rurality on stage of diagnosis of laryngeal cancer has not been examined. However, Sibley et al. (23) reported an association between rurality and health care utilization. Individuals living in the most rural areas are the least likely to be vaccinated against influenza and have a regular physician, while those living in the most urban areas are likely to see a specialist (23).
Socioeconomic status	Studies from Canada have been inconclusive due to methodological limitations (27,33). However, research from the United States shows that patients with lower socioeconomic status are more likely to be diagnosed with advanced-stage laryngeal cancer (24,31,34). Lower income is also associated with a decreased likelihood of having an influenza vaccination, visiting a specialist, and having a regular physician (23). Similarly, individuals who had less than high school education are less likely to have contacted a doctor than those with university or college education (103). In Canada, however, income is not associated with hospitalization or visiting any health professional (103).
Co-morbidity status	Having at least one alcohol- or tobacco-related co-morbidity is associated with being diagnosed with advanced-stage laryngeal cancer (26). Compared to those without chronic conditions, individuals with one or more chronic conditions are more likely to be hospitalized or contact a doctor (103).

Table 3-3. (Continued)

Covariate	Rationale
Laryngeal cancer subsite	Laryngeal cancer subsite is associated with stage at diagnosis, with supraglottic cancer more likely to be diagnosed at an advanced stage than glottic cancer (10,14,18,19). The symptoms of supraglottic cancer are more alarming (19), which may affect how readily individuals seek medical care.

3.9.1 Age and Sex

Age and sex were ascertained using data from the RPDB. Subjects' ages were calculated from the date of birth to the study index date. As described previously, the index date for patients in the laryngeal cancer cohort was the date of diagnosis documented in the OCR, while the index date for subjects in the comparison cohort matched the index dates of the laryngeal cancer patients. Age was initially examined to establish whether it should be characterized as a continuous or categorical variable for regression analyses. This determination was based on whether the assumption of linearity was satisfied (88). Sex was a dichotomous variable, where subjects were classified as male or female.

3.9.2 Rurality

The Rurality Index for Ontario (RIO) 2008 Basic was used to assign rurality to subjects' place of residence. This index is a measure of the relative degree of rurality of Ontario census subdivisions (CSDs) and was selected because the factors used to operationalize rurality relate to the availability and accessibility of health services. The Rurality Index for Ontario was developed for the Ontario Medical Association and the Ministry of Health and Long-Term Care to help structure policies and incentive programs for physicians practising in rural communities (104-106). The current version of the index, RIO 2008 Basic, is a scale ranging from 0 to 100, in which a higher score indicates a greater degree of rurality. RIO 2008 Basic is based on three components: population size and density, travel time to the nearest basic referral centre, and travel time to the nearest

advanced referral centre (106). Based on the importance of these factors towards characterizing rurality, travel time to a basic referral centre has the most weight while travel time to an advanced referral centre is given the least weight. Each component is measured relative to the median values of Ontario, summed, and transformed to produce RIO 2008 Basic scores for all of the 2006 CSDs (106).

Using an ICES macro (107), RIO 2008 Basic scores were assigned based on the census subdivision corresponding to the postal code at 27 months before the index date (from PSTLYEAR file). RIO 2008 Basic scores were categorized as rural, large urban, and small urban for the statistical analyses. RIO 2008 Basic scores of 40 or greater were classified as rural, which is in accordance with the cut-off established by the MOHLTC (104). Rural areas typically have a maximum population of about 20,000 (108). Similar to previous studies using Ontario's health administrative data, RIO2008 Basic scores between 0 and 9 were classified as large urban (108,109),while scores between 10 and 39 were classified as small urban. The populations for large urban areas range between 100,000 to 2.5 million people (108).

3.9.3 Socioeconomic Status

Socioeconomic status was assessed at 27 months before the index date, based on the postal code and associated dissemination area documented in the PSTLYEAR files. Neighbourhood income quintile was the area-level measure of socioeconomic status used in the current study. This measure is derived by Statistics Canada using census data. Neighbourhood income quintile is based on the average income per person-equivalent in a dissemination area (i.e. total household income divided by the number of person-equivalents) (83,110). Person-equivalents are a weighted total of the number of households in a dissemination area and are used to adjust for household size (110). Neighbourhood income

quintiles for dissemination areas are determined within a census metropolitan area or census agglomeration. This approach helps reduce the effect of variations in cost of living on income (83). For the current study, neighbourhood income quintiles were obtained from the 2001 and 2006 PCCF files by implementing an ICES macro (84). The 2001 dissemination area-level income quintiles were assigned to subjects assessed in 2002 and 2003, while the 2006 income quintiles were used for subjects assessed from 2004 and onwards.

3.9.4 Co-morbidity Status

Co-morbidity status was determined using Aggregated Diagnosis Groups (ADGs), which is a component of the Johns Hopkins University Adjusted Clinical Groups (ACG) Case-Mix System. This case-mix system utilizes health administrative data to measure the health status and health resource use in a population (111,112). The validity of using the ACG Case-Mix System for Canadian health administrative data has been demonstrated previously (111,113,114). The ACG Case-Mix System assigns diagnostic codes (ICD-9, ICD-9-CM, ICD-10) in the health administrative data to one of the 32 ADGs. The ADGs are clusters of morbidities that have similar duration, severity, diagnostic certainty, etiology, and requirements for specialty care (111,112). ADGs are the component of the case-mix system that measures co-morbidity, while another component of the system measures expected use of health resources by grouping age, sex, and combinations of diagnoses (113).

As per the contract between ICES and developers of the Johns Hopkins University Adjusted Clinical Groups Case-Mix System software, a description of the study was submitted to developers, through ICES, prior to using the software. The ICES macro was used to obtain the ADGs based on diagnostic codes in the OHIP claims database and the CIHI-DAD (115). Based on the precedent of previous research, an individual's ADGs were

aggregated to characterize co-morbid illness burden. In the current study, the total number of distinct ADGs was categorized as 0 to 3, 4 to 5, 6 to 7, 8 to 9, and ≥ 10 ADGs.

3.9.5 Laryngeal Cancer Subsite

It was necessary for subsite to be considered in the analyses for Objective 2 because stage at diagnosis varies significantly between glottic and supraglottic cancers. This difference between the two subsites is largely attributed to the stage at which symptoms become apparent and the nature of symptoms (10,14,18,19). The subsite of laryngeal cancer was determined from the ICD-9 diagnostic code recorded for the primary cancer site in the Ontario Cancer Registry. Glottic and supraglottic cancers were identified using the ICD-9 codes 1610 and 1611, respectively.

3.10 Statistical Analyses

Separate descriptive and multivariable analyses were conducted to compare usual health care utilization between laryngeal cancer patients and the general population, and examine the associations between usual health care utilization and stage at diagnosis for laryngeal cancer. The analyses for the matched case-control study in Objective 1 included a sample of 10,212 subjects, while the analyses for Objective 2 was conducted on a sample of 1,702 laryngeal cancer patients. All statistical analyses were performed using SAS® (Version 9.2, SAS Institute Inc., Cary, North Carolina) at the ICES@Queen's Health Services Research Facility.

3.10.1 Preliminary Analyses

3.10.1.1 Comparison of Laryngeal Cancer Patient Characteristics

Demographic and clinical characteristics of patients in the laryngeal cancer cohort and laryngeal cancer patients excluded from the study population were compared to

determine if there were any systematic differences between the two groups. Distributions of these characteristics were compared using the chi-square test of independence.

3.10.1.2 Distribution of Health Care Encounters by LHIN

As discussed in Section 3.3.3, there were concerns regarding the completeness of physician services captured in the OHIP claims database. Thus, to address this issue the number of health care encounters was compared among LHINs for subjects in the comparison cohort and laryngeal cancer cohort. Since the distribution of the number of health care encounters was positively-skewed, the Kruskal-Wallis method for non-parametric analysis of variance was used for the comparison of medians across the 14 LHINs. If the number of health care encounters varied significantly among the LHINs, *a priori* comparisons were performed. Specifically, the South East, North East, Waterloo Wellington, and Hamilton Niagara Haldimand Brant LHINs were compared to the other ten LHINs (represented as one group) because of the prevalence of alternate funding plans in these regions. The Wilcoxon rank sum test, with a Bonferroni correction, was used to compare the median number of health care encounters of each LHIN to the median of the other ten LHINs. For the laryngeal cancer cohort, the distribution of early- and advanced-stage disease was also compared between the four LHINs of concern and the other ten LHINs using the chi-square test of independence.

3.10.2 Descriptive Analyses

Descriptive analyses were performed to examine the distribution of the usual health care utilization variables, baseline characteristics, which include age, sex, rurality, socioeconomic status, and co-morbidity status, as well as disease subsite for laryngeal cancer patients. Descriptive statistics for these study variables were presented individually for the comparison cohort, the laryngeal cancer cohort, and for each of the four stage groups of

laryngeal cancer patients. For continuous variables, measures of central tendency and dispersion were described, while frequency distributions were described for categorical variables. Distributions of the usual health care utilization variables and baseline characteristics were also compared between study groups. These variables were compared between the laryngeal cancer cohort and the comparison cohort in Objective 1 using univariate conditional logistic regression. This approach was selected over traditional two-sample analyses because it allowed for the 5:1 matching to be accounted for in the analyses (88). For Objective 2, the study variables were compared across the four laryngeal cancer stage groups using the Kruskal-Wallis method for non-parametric analysis of variance for continuous variables or the one-way analysis of variance for normally distributed continuous variables. For categorical variables, the chi-square test of independence and the Cochran-Armitage trend test or Mantel-Haenszel chi-square test for linear association were performed.

3.10.3 Multivariable Analyses

Conditional logistic regression was used to estimate the adjusted odds ratios (ORs) for the association between usual health care utilization and the risk of laryngeal cancer in Objective 1 analyses. Estimates produced by this model accounted for the matching between cases and controls (88). To investigate the strength of association between the measures of usual health care utilization and stage at diagnosis in Objective 2, log binomial regression was utilized. Log binomial regression was selected for this analysis because the outcome, stage at diagnosis, was examined as a dichotomous variable. In addition, this model provided unbiased estimates of the adjusted relative risks (RRs) for the retrospective cohort study (116).

For both study objectives, preliminary unadjusted regression analyses were performed to determine which usual health care utilization variables and covariates to include

in the multivariable models. A liberal significance level of 0.25 for the association between usual health care use measures and the outcome was used to identify the measures of interest. Similarly, covariates were considered as potential confounders in the multivariable analyses if they were associated with the outcome at a significance level of 0.20. The significance level used to select the usual health care utilization variables was more liberal than that used to select covariates because usual health care use was the study's exposure of interest.

3.10.3.1 Assessment of the Linearity Assumption of Regression Analyses

Prior to regression analyses, the frequency of health care encounters and age were investigated to determine whether these should be characterized as continuous or categorical variables. As mentioned previously, this was necessary to consider because regression analyses assume that the relationship between the predictor variable and the log odds (logistic regression) or log relative risk (log binomial regression) is linear (88,117). Using the methods described by Hosmer and Lemeshow (88), the categorical classifications (i.e. quintiles) of the frequency of health care encounters and age were analysed in unadjusted models. The parameter estimates were plotted against the log odds or log relative risk to assess linearity. For Objective 2, it was also possible to plot the results of univariate log binomial regression for the continuous representation of the variables using a locally weighted scatterplot smoothing method (88,118,119). This is a non-parametric local regression method, which fits a smooth relationship between independent and dependent variables by estimating a linear or quadratic function for a small proportion of data around a point (118,119). The continuous characterizations of the number of health care encounters and age were chosen if the relationship appeared linear in the plots. Otherwise, the categorical representation of these variables was more appropriate for multivariable regression.

3.10.3.2 Model Selection

Since there were multiple usual health care utilization variables of interest, it was important to determine whether these measures were independent and should be modelled together or individually in multivariable regression analyses. Models for each significant utilization measure were compared to the models with all utilization measures. These models were fully adjusted for all significant covariates. If the effect estimates were similar between models, then the model that included the usual health care utilization variables together was selected. Individual models for health care utilization were considered where the model results differed by 10% or greater.

3.10.3.3 Assessment of Confounding

Age, sex, rurality, socioeconomic status, and co-morbidity status were identified as potential confounders *a priori*. Two strategies that can be used to select the covariates that must be controlled are stepwise selection and the change-in-estimate approach. Stepwise selection identifies confounders based on the association between the covariate and the outcome. In contrast, the change-in-estimate approach emphasizes the effect of the covariate on the association between the independent variable of interest and the outcome (120). Since multiple variables were used to characterize usual health care utilization in the current study, the change-in-estimate approach was difficult to use. This is because the set of confounders identified using this approach may vary, depending on the specific exposure-outcome relationship that is being examined within a model. Therefore, a backwards, stepwise selection strategy was employed to select confounders.

Using this method, all potential confounders were included in a multivariable model with the usual health care utilization variables of interest. The relationship between each covariate and the outcome were assessed and the least significant covariate was removed from the multivariable model. This process was repeated until the covariates remaining in

the model were associated with the outcome at a 0.15 significance level. The liberal cut-off was used to avoid under selection of confounders. If, however, the total change-in-estimate between the reduced model and the fully adjusted model was greater than 10%, the covariates that had been removed were further examined and retained in the final model where appropriate.

It is important to note that for the case-control study in Objective 1, age, sex, and geographic area were matching variables. As such, potential confounding by these variables was inherently adjusted by using conditional logistic regression analyses. However, there was the potential for age to confound the associations of interest because matching was within five years. Thus, the continuous representation of age was included in conditional multivariable regression analyses if there was a significant difference in age between the laryngeal cancer cohort and the comparison cohort to check if there was residual confounding. Age was included in the model, if the effect estimates of interest changed significantly.

3.10.3.4 Effect Modification

As determined *a priori*, the analyses for Objective 2 were stratified by laryngeal cancer subsite to assess effect modification. Initially, the unadjusted effect estimates for the association between each usual health care utilization variable and stage at diagnosis were examined for patients with glottic cancer and for those with supraglottic cancer. If the effect estimates were substantially different between the two groups, then the final multivariable model adjusted for confounding was also stratified by subsite.

3.10.4 Sensitivity Analysis

For Objective 2, a sensitivity analysis was conducted to assess potential misclassification of stage at diagnosis. As stage at diagnosis is only captured at RCCs, the staging data recorded at the RCC may not represent the initial presentation of stage at

diagnosis. Therefore, the distribution of the length of time between the date of diagnosis and registration at a RCC was examined to identify the average length of time in which stage is reported. Laryngeal cancer is a variable disease and there is no evidence on the rate of tumour growth. Therefore, the distribution of stage at diagnosis was examined among patients where length of time from diagnosis to RCC registration exceeded 30 days, 60 days, and 90 days. If there were a significant number of patients with advanced-stage disease in these groups, these patients were excluded for the sensitivity analysis. Multivariable regression analyses for the associations between the usual health care utilization variables and stage at diagnosis would be performed for the subgroup to assess the effects of misrepresentation of the outcome.

3.10.5 Regression Diagnostics

Collinearity among the usual health care utilization variables was assessed for the final multivariable conditional logistic regression model and the final multivariable log binomial regression models. If any of the usual health care utilization variables were highly correlated, modelling these variables separately was considered. To assess model fit, residual analysis, outlier assessment, analysis of influential points, and the Hosmer-Lemeshow goodness-of-fit tests were conducted.

3.11 Ethical Considerations

Study ethics approval was obtained from the Health Sciences Research Ethics Board at Queen's University (see Appendix B). Approval was also obtained from the Institute for Clinical Evaluative Sciences and Cancer Care Ontario to access the necessary data for the current study. ICES and CCO are prescribed entities under Ontario's Personal Health Information Protection Act, which means that these organizations can receive and use health information for the purposes of analysis, evaluation, and research. As personal health

information was used in the current study, maintaining the privacy and confidentiality of the data was the primary ethical consideration. To address this concern, all study personnel complied with the privacy and confidentiality policies outlined by ICES and CCO. Additionally, all data were anonymized and only contained an encrypted subject identifier that was not associated with any identifying information. The study dataset was stored on the isolated, secure system at ICES, which is a locked facility that has 24-hour video-surveillance and can only be accessed by authorized personnel.

CHAPTER 4 RESULTS

4.1 Overview

The results of the study analyses are reported in this chapter. The first section presents preliminary analyses comparing the characteristics of patients included in the laryngeal cancer cohort to those who were excluded, as well as examining the distribution of health care encounters by Local Health Integration Network (LHIN). Next, the results for Objective 1 and Objective 2 of the study are presented in Section 4.3 and Section 4.4, respectively. For each study objective, the demographic and clinical characteristics, as well as usual health care utilization are described for the study population. This is followed by the results of the multivariable regression analyses, which compared usual health care utilization between the laryngeal cancer and comparison cohorts (Objective 1), and by stage at diagnosis among the laryngeal cancer cohort (Objective 2). Findings from a sensitivity analysis are also presented for Objective 2. Lastly, regression diagnostics for the multivariable regression models are reported.

4.2 Preliminary Analyses

4.2.1 Comparison of Laryngeal Cancer Patient Characteristics

Table 4-1 presents characteristics of the laryngeal cancer patients who met the study's inclusion criteria. The distribution of glottic and supraglottic cancers varied between patients who were included and excluded from the study, with less supraglottic cancer in the laryngeal cancer cohort. Age at diagnosis (mean [standard deviation, SD]: laryngeal cancer cohort, 65.9 [10.4] years; excluded laryngeal cancer patients, 66.6 [11.7] years; $p = 0.29$) and the sex distribution were not different between the two groups. However, the proportion of patients age 80 years or older was somewhat lower among laryngeal cancer patients included

in the study. Finally, the laryngeal cancer cohort consisted of proportionally more patients from the South West LHIN and fewer patients living in the Mississauga Halton, Toronto Central, and Champlain LHINs compared to the laryngeal cancer patients who were excluded from the study population.

Table 4-1. Characteristics of the study's laryngeal cancer cohort and laryngeal cancer patients who met the inclusion criteria but were excluded from the study population due to missing data.

	Laryngeal Cancer Cohort (*n* = 1,702)		Excluded Laryngeal Cancer Patients (*n* = 360)		
Characteristic	**No.**	**(%)**	**No.**	**(%)**	***p*-value[†]**
Cancer subsite					
Glottis	1,205	(70.80)	232	(64.44)	0.02
Supraglottis	497	(29.20)	128	(35.56)	
Age at date of diagnosis					
40 to 49 years	104	(6.11)	24	(6.67)	0.02
50 to 59 years	369	(21.68)	81	(22.50)	
60 to 69 years	590	(34.67)	110	(30.56)	
70 to 79 years	476	(27.97)	90	(25.00)	
≥ 80 years	163	(9.58)	55	(15.28)	
Sex					
Male	1,434	(84.25)	303	(84.17)	0.97
Female	268	(15.75)	57	(15.83)	
Local Health Integration Network (LHIN)					
Erie St. Clair	116	(6.82)	23	(6.42)	< 0.0001
South West	199	(11.69)	*	*	
Waterloo Wellington	94	(5.52)	*	*	
Hamilton Niagara Haldimand Brant	212	(12.46)	33	(9.22)	
Central West	66	(3.88)	25	(6.98)	
Mississauga Halton	85	(4.99)	36	(10.06)	
Toronto Central	130	(7.64)	43	(12.01)	
Central	148	(8.70)	35	(9.78)	
Central East	153	(8.99)	38	(10.61)	
South East	75	(4.41)	16	(4.47)	
Champlain	184	(10.81)	55	(15.36)	
North Simcoe Muskoka	71	(4.17)	21	(5.87)	
North East	129	(7.58)	15	(4.19)	
North West	40	(2.35)	*	*	

* Values were suppressed because the counts were less than 10.
[†] Chi-square test for association.

4.2.2 Distribution of Health Care Encounters by LHIN

The distribution of health care encounters was examined by LHIN to assess the completeness of physician billings in the OHIP claims database and determine if the analyses for Objective 1 and Objective 2 would be affected. The focus was on four LHINs, which were identified *a priori* because of the large number of physicians on an alternate funding plan (AFP). These include the South East, North East, Waterloo Wellington, and Hamilton Niagara Haldimand Brant LHINs. These four LHINs will be referred to as AFP LHINs, while the other ten LHINs will be denoted as non-AFP LHINs.

Among the comparison cohort, the median number of health care encounters for persons in non-AFP LHINs was 26 (interquartile range, IQR: 11–47) encounters. Individuals in three of the AFP LHINs had significantly fewer visits compared to those residing in non-AFP LHINs (median [IQR]: 20 [9–40] encounters; $p = 0.0001$). The exception was the Hamilton Niagara Haldimand Brant LHIN, where the median number of health care visits was 25 (IQR: 11–45; $p = 0.33$). The distribution of health care encounters found in the general population suggested that there may be underreporting of health care visits in the AFP LHINs. However, this concern was likely mitigated in the study design by matching the laryngeal cancer cohort and the comparison cohort by subLHIN and should not bias the analyses for Objective 1.

For laryngeal cancer patients living in non-AFP LHINs, the median was 20 (IQR: 9–36) health care encounters and the frequency of visits was not significantly different for any of the AFP LHINs compared to non-AFP LHINs ($p = 0.50$; see Table 4-2). Thus, undercounting health care encounters did not appear to be an issue for Objective 2 analyses. Additionally, the proportion of Stage III or IV cancer was similar for patients from AFP LHINs and those from non-AFP LHINs (40.5% versus 38.2%; $p = 0.45$).

Table 4-2. Frequency of health care encounters by LHIN for the laryngeal cancer cohort.

		Number of Health Care Encounters	
Local Health Integration Network (LHIN)	***n***	**Median**	**Interquartile Range**
Non-AFP	1,184	20	9–36
Waterloo Wellington	94	21	5–37
Hamilton Niagara Haldimand Brant	217	19	10–38
South East	79	23	8–38
North East	128	23.5	12–34.5

4.3 Objective 1: Comparison of Usual Health Care Utilization between Laryngeal Cancer Patients and the General Population

4.3.1 Characteristics of Laryngeal Cancer Patients and the General Population

A total of 1,702 patients with an incident laryngeal cancer were matched to 8,510 individuals from the general population, based on age, sex, and subLHIN. The distributions of demographic and clinical characteristics for the laryngeal cancer cohort and the comparison cohort are presented in Table 4-3. The mean age of the study population was 66 years. By design, the age of laryngeal cancer patients (mean [SD]: 65.9 [10.4] years) and the controls (mean [SD]: 66.0 [10.5] years; $p < 0.0001$) were roughly equal due to matching, although the 0.1-year mean difference was statistically significant because of the large sample size. Since sex was also a matching variable, the distribution was identical for laryngeal cancer patients and the controls. The ratio of males to females in the study population was approximately five to one, which corresponds with the sex distribution of laryngeal cancer reported in the literature. Both rurality and neighbourhood income quintile were ecologic variables. As a result, the distributions of these variables did not vary between the laryngeal cancer cohort and the comparison cohort because there was matching by geographic region. The majority of the study population resided in large urban areas. With regards to socioeconomic status, a slightly greater proportion of individuals were in the lowest two general population-derived income quintiles. Finally, a greater number of

individuals in the general population were in the highest co-morbidity group (i.e. ≥ 10 ADGs) compared to patients with laryngeal cancer. However, the median number of ADGs was the same in the laryngeal cancer cohort and the comparison cohort (median: 6 ADGs).

Table 4-3. Demographic and clinical characteristics of laryngeal cancer patients and the general population.

	Laryngeal Cancer Cohort (*n* = 1,702)		Comparison Cohort (*n* = 8,510)		
Characteristic	**No.**	**(%)**	**No.**	**(%)**	***p*-value***
Age at study index date[†]					
40 to 49 years	104	(6.1)	557	(6.5)	0.03
50 to 59 years	369	(21.7)	1,788	(21.0)	
60 to 69 years	590	(34.7)	2,878	(33.8)	
70 to 79 years	476	(28.0)	2,421	(28.4)	
≥ 80 years	163	(9.6)	866	(10.2)	
Sex[†]					
Male	1,434	(84.3)	7,170	(84.3)	----
Female	268	(15.7)	1,340	(15.7)	
Rurality					
Large urban (0 ≤ RIO ≤ 9)	1,051	(61.7)	5,304	(62.4)	0.31
Small urban (10 ≤ RIO ≤ 39)	420	(24.7)	2,115	(24.9)	
Rural (RIO ≥ 40)	231	(13.6)	1,081	(12.7)	
Neighbourhood income quintile					
Q1 (low)	381	(22.4)	2,023	(23.8)	0.54
Q2	398	(23.4)	1,855	(21.9)	
Q3	330	(19.4)	1,669	(19.7)	
Q4	312	(18.4)	1,522	(18.0)	
Q5 (high)	278	(16.4)	1,407	(16.6)	
Co-morbidity status					
0 to 3 ADGs	427	(25.1)	2,015	(23.7)	0.02
4 to 5 ADGs	329	(19.3)	1,576	(18.5)	
6 to 7 ADGs	344	(20.2)	1,559	(18.3)	
8 to 9 ADGs	258	(15.2)	1,353	(15.9)	
≥ 10 ADGs	344	(20.2)	2,007	(23.6)	

* Univariate conditional logistic regression.
[†] Variables used for matching laryngeal cancer cohort and comparison cohort, plus subLHIN.

4.3.2 Usual Health Care Utilization for Laryngeal Cancer Patients and the General Population

Table 4-4 provides a description of usual health care utilization for the laryngeal cancer cohort and the comparison cohort. Laryngeal cancer patients had significantly fewer health care encounters over a two-year period than the general population (mean [SD]: laryngeal cancer cohort, 26.1 [23.8] visits; comparison cohort, 33.9 [35.0] visits; $p < 0.0001$). The number of health care encounters was positively-skewed, where the median values for the laryngeal cancer cohort and comparison cohort were 20 (IQR: 9–36) and 25 (IQR: 11–46) visits, respectively. On average, office-based visits accounted for 93.9% and 92.8% of the health care encounters by individuals in the laryngeal cancer cohort and the control group, respectively. Among the laryngeal cancer patients and the controls, 37.9% and 47.6%, respectively, had at least one emergency room visit in a two-year period. Hospitalizations within a two-year period were present for 43.5% and 49.4% of the laryngeal cancer cohort and comparison cohort, respectively. Of the individuals who had three or more visits to a general physician or family physician (GP/FP) during the two-year period, a similar proportion of laryngeal cancer patients and controls experienced high continuity of care. However, approximately 12% of the study population saw a GP/FP fewer than three times. Also, enrolment in a primary care model was not common among individuals in the laryngeal cancer cohort or the comparison cohort.

As shown in Table 4-4, use of preventive services varied between the laryngeal cancer cohort and the comparison cohort. Annual physical examination status differed significantly between the two study groups, with controls more likely to have had an examination. However, less than a quarter of the study population had a physical examination during a two-year period. Influenza vaccination, on the other hand, was similar for laryngeal cancer patients and controls, with approximately 52% receiving an influenza

vaccination. For the three types of cancer screening, only use of breast cancer screening was significantly different between the laryngeal cancer cohort and the comparison cohort. Interestingly, more female laryngeal cancer patients had mammography than the general female population. Examination of an individual's overall tendency to use preventive health care, using the preventive services index, showed that over one-third of laryngeal cancer patients and the general population did not utilize any of the preventive services for which they were eligible. However, a greater proportion of the laryngeal cancer cohort had more than half of their eligible preventive health care compared to the comparison cohort.

Table 4-4. Usual health care utilization for laryngeal cancer patients and the general population.

Usual Health Care Utilization Variables	Laryngeal Cancer Cohort (*n* = 1,702)		Comparison Cohort (*n* = 8,510)		
	No.	(%)	No.	(%)	*p*-value*
Number of health care encounters					< 0.0001
0 to 8 encounters	584	(22.6)	1,726	(20.3)	
9 to 19 encounters	448	(26.3)	1,806	(21.2)	
20 to 32 encounters	371	(21.8)	1,676	(19.7)	
33 to 52 encounters	305	(17.9)	1,628	(19.1)	
≥ 53 encounters	194	(11.4)	1,674	(19.7)	
Continuity of care					0.75
High (UPC index ≥ 0.75)	1,032	(68.4)	5,121	(68.7)	
Low (UPC index < 0.75)	476	(31.6)	2,332	(31.3)	
Enrolled in a primary care model – Yes	163	(9.6)	859	(10.1)	0.47
Preventive service use – Yes					
Annual physical examination	339	(17.1)	1,367	(21.7)	< 0.0001
Influenza vaccination	883	(51.9)	4,437	(52.1)	0.84
Colorectal cancer screening	360	(23.9)	1,740	(23.3)	0.56
Breast cancer screening	83	(55.3)	322	(44.6)	0.02
Cervical cancer screening	72	(44.2)	322	(38.6)	0.13
Preventive services index (% of eligible services used)					
0%	596	(35.0)	3,015	(35.3)	0.008
> 0% and ≤ 50%	667	(39.2)	3,597	(42.3)	
> 50% and < 100%	352	(20.7)	1,555	(18.3)	
100%	87	(5.1)	343	(4.0)	

* Univariate conditional logistic regression.

4.3.3 Multivariable Analyses

Conditional logistic regression was used to examine whether individuals who are diagnosed with laryngeal cancer have different patterns of usual health care utilization than those without a laryngeal cancer diagnosis due to the matched-design of the case-control study. The analyses described in Section 4.3.2 showed that the number of health care encounters and overall use of preventive services were significantly different between subjects in the laryngeal cancer cohort and the comparison cohort at the 0.25 significance level specified *a priori*.

Of the demographic and clinical characteristics examined in Section 4.3.1, only age and co-morbidity status were significantly associated with laryngeal cancer status at the defined significance level of 0.20. Residual confounding by age (after matching with five-year increments) was examined in conditional logistic regression. The effect estimates from conditional logistic regression models with and without age as a continuous predictor variable were compared. The adjusted odds ratios for the number of health care encounters and the overall use of preventive services differed by 1% or less between the models. This finding justified using a conditional logistic regression model without including age as an independent variable to further adjust for confounding. Thus, the effects of the frequency of health care encounters and preventive services use on laryngeal cancer status were investigated in the multivariable analyses, with co-morbidity status as a potential confounder.

4.3.3.1 Assessment of the Linearity Assumption

The continuous measure of the number of health care encounters was examined to determine if the linearity assumption of regression analyses was satisfied. The number of health care encounters variable was categorized into quintiles based on the distribution of the comparison cohort. These categories were 0 to 8, 9 to 19, 20 to 32, 33 to 52, and ≥ 53 encounters. Figure 4-1 shows the results of fitting the categorical representation in a conditional logistic regression model, where the highest quintile was the reference group. The plotted results show that the relationship between number of health care encounters and the log odds (i.e. logit) of laryngeal cancer was not linear. Based on these initial investigations, the categorical classification of the number of health care encounters was more appropriate for subsequent regression analyses.

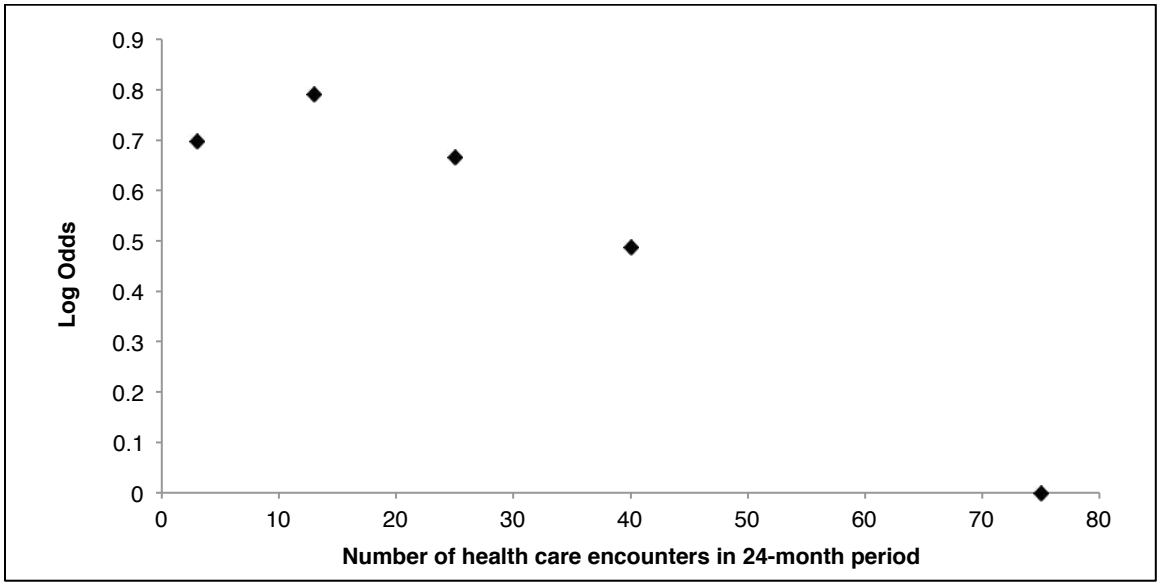

Figure 4-1. Log odds of laryngeal cancer by the number of health care encounters, represented as a categorical variable in unadjusted conditional logistic regression.

4.3.3.2 Unadjusted Models

Table 4-5 presents the unadjusted odds ratios (ORs) for usual health care utilization by the laryngeal cancer cohort compared to the comparison cohort. The results of the conditional logistic regression analyses were interpreted as 'exposure odds ratios' rather than the usual 'disease odds ratios'. Overall, laryngeal cancer patients were significantly more likely to have fewer health care encounters in a two-year period than the general population. For overall preventive services use, the direction of the odds ratios indicated that laryngeal cancer patients were more likely than the general population to utilize the eligible preventive services.

Table 4-5. Unadjusted odds ratios for usual health care utilization by laryngeal cancer patients and the general population.

Usual Health Care Utilization Variables	Laryngeal Cancer and Comparison Cohorts (*n* = 10,212)		
	Unadjusted OR*	(95% CI)	*p*-value
Number of health care encounters			
0 to 8 encounters	2.01	(1.66, 2.44)	< 0.0001
9 to 19 encounters	2.21	(1.84, 2.65)	
20 to 32 encounters	1.95	(1.61, 2.35)	
33 to 52 encounters	1.63	(1.34, 1.97)	
≥ 53 encounters	1.00	(Reference)	
Preventive services index (% of eligible services used)			
0%	0.77	(0.60, 1.00)	0.007
> 0% and ≤ 50%	0.73	(0.56, 0.93)	
> 50% and < 100%	0.89	(0.69, 1.16)	
100%	1.00	(Reference)	

* Univariate conditional logistic regression.

4.3.3.3 Model Selection and Assessment of Confounding

Three models were assessed to determine if it was appropriate to include the usual health care utilization variables together in a model or if separate regression analyses for each utilization variable was warranted. Three multivariable conditional logistic regression models were fitted for both utilization variables, the number of health care encounters only, and the preventive services index only, and were adjusted for the potential confounding effects of co-morbidity status (see Table 4-6).

The adjusted odds ratios for usual health care utilization differed by less than 4% between the models with individual utilization measures and the model with both utilization measures. The precision of the effect estimates also remained stable for the three regression models. Therefore, the number of health care encounters and the overall use of preventive services were included in the same model for the final multivariable regression analyses. After considering model selection, co-morbidity status was retained in the final model, using a backwards, stepwise approach for confounder selection, because it was significantly associated with disease status ($p = 0.04$). Furthermore, the adjusted effect estimates for the number of health care encounters (Model 1 in Table 4-6) were stronger than the unadjusted effect estimates (Table 4-5), differing by as much as 24%. This demonstrated the confounding effect of co-morbidity status on the associations of interest.

Table 4-6. Adjusted odds ratios for usual health care utilization by laryngeal cancer patients versus the general population, from models where usual health care utilization variables are included together or individually.

Usual Health Care Utilization Variables	Model 1† (*n* = 10,212)		Model 2† (*n* = 10,212)		Model 3† (*n* = 10,212)	
	Adjusted OR* (95% CI)	*p*-value	Adjusted OR* (95% CI)	% Change‡	Adjusted OR* (95% CI)	% Change‡
Number of health care encounters						
0 to 8 encounters	2.83 (2.16, 3.71)	< 0.0001	2.78 (2.12, 3.63)	-1.9	----	----
9 to 19 encounters	2.72 (2.17, 3.40)		2.73 (2.18, 3.41)	0.4	----	----
20 to 32 encounters	2.16 (1.76, 2.65)		2.18 (1.77, 2.68)	0.9	----	----
33 to 52 encounters	1.70 (1.40, 2.08)		1.71 (1.41, 2.09)	0.7	----	----
≥ 53 encounters	1.00 (Reference)		1.00 (Reference)	----	----	----
Preventive services index (% of eligible services used)						
0%	0.72 (0.55, 0.94)	0.003	----	----	0.72 (0.56, 0.94)	-0.1
> 0% and ≤ 50%	0.73 (0.57, 0.94)		----	----	0.70 (0.55, 0.91)	-4.0
> 50% and < 100%	0.91 (0.70, 1.19)		----	----	0.89 (0.68, 1.16)	-2.2
100%	1.00 (Reference)		----	----	1.00 (Reference)	----

* Conditional logistic regression (matched by age, sex, and subLHIN) adjusted for co-morbidity status, and the other usual health care utilization variable in the model, if applicable.

† Model 1: number of health care encounters + overall preventive services use (i.e. preventive services index; Model 2: number of health care encounters only; Model 3: overall preventive services use only.

‡ Calculated as the percentage change in adjusted odds ratio versus Model 1.

4.3.3.4 Final Model

Model 1 in Table 4-6 presents the adjusted odds ratios of the association between usual health care utilization and having a diagnosis of laryngeal cancer. Laryngeal cancer patients were significantly more likely to have fewer health care encounters in a two-year period compared to the general population ($p < 0.0001$). An overall trend in the odds ratios was observed, which showed that, compared to the general population, the likelihood of laryngeal cancer patients using less than the highest quintile of health care visits increased as the number of health care encounters decreased. Laryngeal cancer patients had 2.8 (95% confidence interval, CI: 2.2, 3.7) times the odds of having eight or fewer health care visits in a two-year period (versus 53 or more visits) in comparison to the general population. The overall preventive services use was also significantly associated with laryngeal cancer status ($p = 0.003$). Laryngeal cancer patients were generally more likely than the general population to utilize the preventive services for which they were eligible. The odds of using less than half of the eligible preventive services, versus all preventive services, was about 30% less for laryngeal cancer patients compared to the general population. However, there was no difference in the likelihood of using more than half of the eligible preventive services between laryngeal cancer patients and the general population.

4.4 Objective 2: Association between Usual Health Care Utilization and Stage at Diagnosis among Laryngeal Cancer Patients

4.4.1 Characteristics of Laryngeal Cancer Patients by Stage at Diagnosis

Among the laryngeal cancer cohort, 39.6%, 21.6%, 18.0%, and 20.8% were diagnosed with Stage I, II, III, and IV disease, respectively. Table 4-7 provides a description of the demographic and clinical characteristics of the laryngeal cancer patients by stage group. Overall, 70.8% of patients were diagnosed with glottic cancer, while 29.2% had supraglottic cancer. There was a significant trend between laryngeal cancer subsite and stage at diagnosis, which showed that the proportion of supraglottic cancer was lowest for Stage I disease and highest for Stage IV disease. Compared to patients with Stage II, III, or IV laryngeal cancer, those with Stage I disease were older and had a higher ratio of males to females. The average age at diagnosis was 67.1 (SD: 10.2) years, 65.1 (SD: 10.8) years, 65.7 (SD: 10.6) years, and 64.6 (SD: 10.1) years for Stage I, II, III, and IV patients, respectively ($p = 0.0009$). There was no significant variation in the rurality of laryngeal cancer patients' residence among the four stage groups. Overall, 13.6% of patients lived in rural areas, while the majority were from large urban areas (61.7%). A significant trend was also observed for socioeconomic status across stage groups. The proportion of laryngeal cancer patients living in the lowest income area was about 7% greater for Stage III or IV patients versus those with Stage I disease. Examination of co-morbidity status by stage showed that patients with Stage IV laryngeal cancer had fewer reported co-morbidities. The trend between co-morbidity status and stage at diagnosis showed that the proportion of patients with the fewest co-morbidities (i.e. 0 to 3 ADGs) increased with stage.

Table 4-7. Disease, demographic, and clinical characteristics by stage at diagnosis of laryngeal cancer.

Characteristics		Stage I (*n* = 674) %	Stage II (*n* = 368) %	Stage III (*n* = 306) %	Stage IV (*n* = 354) %	*p*-value*
Cancer subsite	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
Glottis		94.1	76.1	55.6	34.2	< 0.0001
Supraglottis		5.9	23.9	44.4	65.8	
Age at diagnosis (*n* = 1,702)	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
40 to 49 years		4.7	8.4	6.9	5.7	0.0005
50 to 59 years		18.1	23.4	20.9	27.4	
60 to 69 years		35.2	34.0	34.0	35.0	
70 to 79 years		31.0	23.6	30.4	24.6	
≥ 80 years		11.0	10.6	7.8	7.3	
Sex	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
Male		88.0	82.3	80.7	82.2	0.004
Female		12.0	17.7	19.3	17.8	
Rurality	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
Large urban (0 ≤ RIO ≤ 9)		61.9	61.4	58.2	65.0	0.81
Small urban (10 ≤ RIO ≤ 39)		24.9	23.6	26.1	24.0	
Rural (RIO ≥ 40)		13.2	15.0	15.7	11.0	
Neighbourhood income quintile	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
Q1 (low)		18.7	23.8	25.5	25.4	0.02
Q2		25.6	20.5	19.6	25.7	
Q3		18.6	21.3	21.2	17.5	
Q4		18.7	21.0	17.0	16.1	
Q5 (high)		18.4	13.4	16.7	15.3	
Co-morbidity status	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
0 to 3 ADGs		19.9	26.1	25.5	33.6	0.006
4 to 5 ADGs		20.3	19.6	17.7	18.6	
6 to 7 ADGs		24.6	17.4	19.9	15.0	
8 to 9 ADGs		15.4	15.5	14.4	15.0	
≥ 10 ADGs		19.7	21.5	22.6	17.8	

* Mantel-Haenszel chi-square test for linear association or Cochran-Armitage trend test (dichotomous variables).

4.4.2 Usual Health Care Utilization for Laryngeal Cancer Patients by Stage at Diagnosis

Table 4-8 presents usual health care utilization for laryngeal cancer patients by stage at diagnosis. The median number of health care encounters during a two-year period for patients with Stage IV laryngeal cancer was 16 visits (IQR: 6–35 visits), which was the lowest among the four stage groups (median [IQR]: Stage I, 22 [12–36] visits; Stage II, 19 [9–35] visits; Stage III, 21 [10–38] visits; $p = 0.0003$). There was also a significant trend between the frequency of health care encounters and stage at diagnosis. Patients with Stage I laryngeal cancer were considerably less likely to have fewer health care visits compared to the other stage groups. Over one-third of Stage IV laryngeal cancer patients had 0 to 8 health care encounters in a two-year period. For both early- and advanced-stage laryngeal cancer patients, office-based visits accounted for over 90% of a patient's encounters, while hospitalizations were the least common type of encounter and accounted for approximately 2% of a patient's visits. An overall decreasing trend was also observed across the four stage groups for high continuity of care. The proportion of laryngeal cancer patients with high continuity of care was up to 9% greater in the Stage I group versus the higher stage groups. It is important to note that, of the four stage groups, Stage IV laryngeal cancer patients were most likely to have two or fewer visits to a GP/FP (18.6%) than those diagnosed with earlier stage cancer (9.5%). Primary care model enrolment did not vary significantly among patients diagnosed with different stages of laryngeal cancer. For all laryngeal cancer patients, 9.6% were enrolled in a primary care model.

As shown in Table 4-8, a significant trend was observed between each of the five preventive services examined and stage at diagnosis. Stage I laryngeal cancer patients were more likely to have an annual physical examination, and had higher usage of influenza vaccination, colorectal cancer screening, breast cancer screening, and cervical cancer

screening. A significant trend with stage was also observed when examining the overall use of preventive services, as measured by the preventive services index. A greater proportion of Stage I laryngeal cancer patients used at least one of the eligible preventive services compared to the other stage groups (72% for Stage I versus as low as 58% for Stage IV).

Table 4-8. Usual health care utilization by stage at diagnosis of laryngeal cancer.

Usual Health Care Utilization Variables		Stage I (*n* = 674) %	Stage II (*n* = 368) %	Stage III (*n* = 306) %	Stage IV (*n* = 354) %	*p*-value*
Number of health care encounters	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
0 to 9 encounters		10.1	27.5	24.2	36.2	0.002
10 to 16 encounters		18.7	16.6	14.7	14.1	
17 to 26 encounters		22.0	17.9	18.6	15.8	
27 to 40 encounters		20.5	17.9	19.9	14.7	
≥ 41 encounters		19.7	20.1	22.6	19.2	
Continuity of care	(*n*)	(*620*)	(*330*)	(*270*)	(*288*)	0.02
High (UPC index ≥ 0.75)		71.9	68.2	63.0	66.3	
Low (UPC index < 0.75)		28.1	31.8	37.0	33.7	
Enrolled in a primary care model –Yes	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
		9.4	9.2	9.8	10.2	0.65
Preventive service use – Yes						
Annual physical examination	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
		23.2	19.0	18.3	16.1	0.005
Influenza vaccination	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	
		57.3	49.7	49.7	45.8	0.0003
Colorectal cancer screening	(*n*)	(*603*)	(*313*)	(*273*)	(*317*)	
		29.0	19.5	20.9	21.1	0.0004
Breast cancer screening	(*n*)	(*39*)	(*32*)	(*35*)	(*44*)	
		82.1	50.0	48.6	40.9	0.0003
Cervical cancer screening	(*n*)	(*43*)	(*41*)	(*31*)	(*48*)	
		67.4	41.5	29.0	35.4	0.0002
Preventive services index (% of eligible services used)	(*n*)	(*674*)	(*368*)	(*306*)	(*354*)	< 0.0001
0%		28.0	37.8	38.6	42.4	
> 0% and ≤ 50%		41.7	39.4	37.6	35.6	
> 50% and < 100%		22.9	19.0	20.6	18.4	
100%		7.4	3.8	3.3	3.7	

* Mantel-Haenszel chi-square test for linear association or Cochran-Armitage trend test (dichotomous variables).

4.4.3 Multivariable Analyses

Multivariable log binomial regression was used to estimate the relative risk of advanced-stage laryngeal cancer for usual health care utilization. From the results of univariate log binomial regression analyses comparing usual health care use between early- and advanced-stage laryngeal cancer patients, the number of health care encounters (p = 0.0007), continuity of care (p = 0.02), and overall use of preventive services (p = 0.04) were included in the multivariable analyses because these measures were significantly associated with stage at diagnosis at a 0.25 significance level. Additionally, the potential confounding variables that were evaluated in multivariable analyses were associated with stage at diagnosis at a 0.20 significance level in unadjusted regression analyses. The confounders that were identified were laryngeal cancer subsite ($p < 0.0001$), age (p = 0.09), sex (p = 0.01), co-morbidity status (p = 0.003), and socioeconomic status (p = 0.14).

4.4.3.1 Assessment of the Linearity Assumption

The linearity assumption of regression analyses was evaluated for the number of health care encounters and age variables. The number of health care encounters variable was categorized into quintiles using the distribution of visits for early-stage (i.e. Stage I or II) laryngeal cancer patients. The five categories were 0 to 9, 10 to 16, 17 to 26, 27 to 40, and $\geq$ 41 encounters, with the highest quintile as the reference category. The categorical and continuous representations of health care encounter frequency were modelled using log binomial regression. Figure 4-2 presents plots of the results of the regression analyses for the categorical classification, as well as for the continuous classification, which was obtained using locally weighted scatterplot smoothing. Both plots demonstrated that the log risk of Stage III or IV laryngeal cancer decreased significantly and then increased with a greater number of health care visits. From these findings, it was determined that the frequency of

health care visits was not linear in the log risk and the categorical representation of the variable was more suitable for multivariable regression analyses.

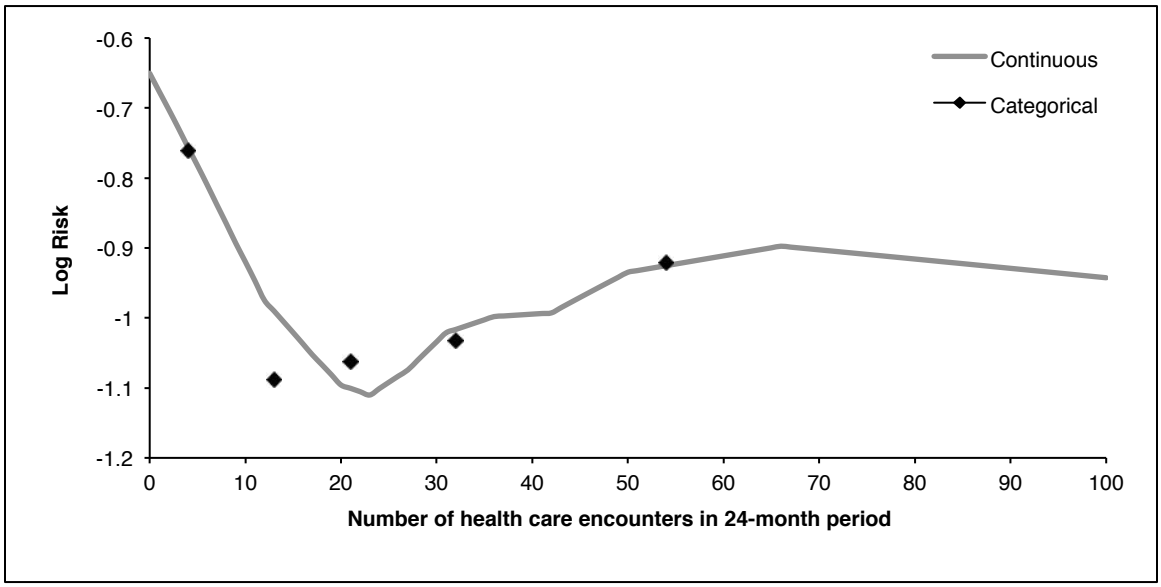

Figure 4-2. Log risk of advanced-stage laryngeal cancer by the number of health care encounters, represented as a categorical and continuous variable in unadjusted conditional logistic regression.

The age categories that were used to examine the linearity assumption were 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥ 80 years, with the 60 to 69 years group as the reference. The estimated coefficients for each age category were obtained from log binomial regression analysis. Figure 4-3 shows the log risk for Stage III or IV laryngeal cancer plotted against the median of each age category, where the results did not support the linearity of age with the log risk. Age, as a continuous variable, was also modelled and the results were plotted versus age at diagnosis using a scatterplot smoothing method (see Figure 4-3). From this plot, the relationship between age and the log risk appeared more linear. However, the linearity of age with the log risk was not conclusively demonstrated, so age was categorized for future regression analyses to ensure that the linearity assumption was not violated.

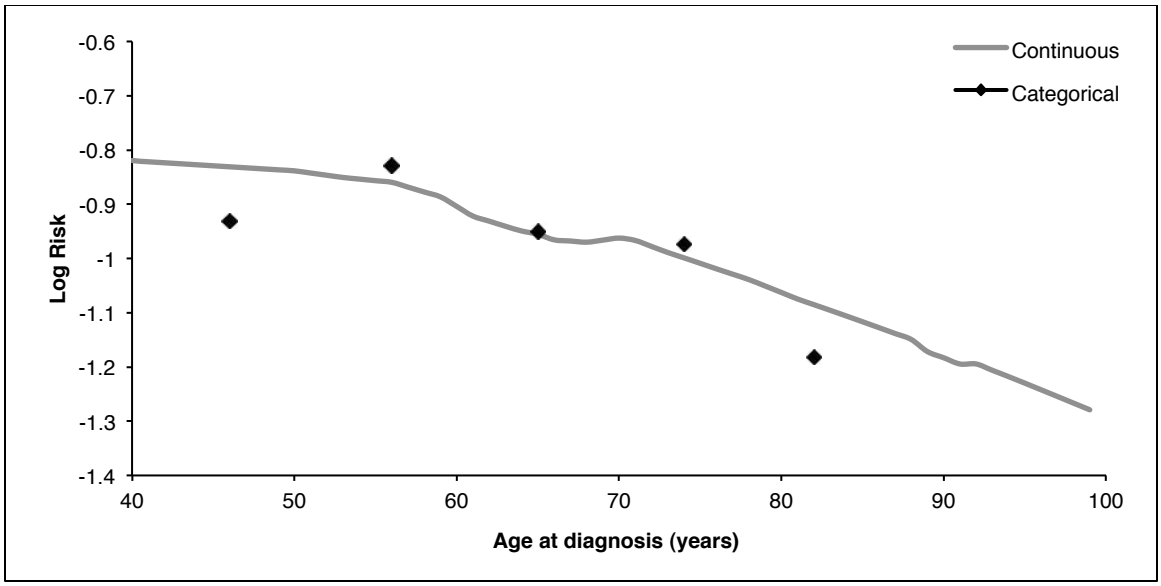

Figure 4-3. Log risk of advanced-stage laryngeal cancer by age at diagnosis, represented as a categorical and continuous variable in unadjusted log binomial regression.

4.4.3.2 Unadjusted Models

The unadjusted relative risks (RRs) for advanced- versus early-stage laryngeal cancer are presented in Table 4-9. Overall, each usual health care utilization variable was statistically significantly associated with stage at diagnosis. This finding corresponded with the results of the bivariate analyses, which analysed stage across all four categories (see Section 0). However, examination of the effect estimates for the number of health care encounters showed that the result was driven by patients who did not use any health care. Laryngeal cancer patients who had low continuity of care had an 18% increased risk of being diagnosed with advanced-stage laryngeal cancer versus those with high continuity of care. For preventive services use, the results were statistically significant in the group who did not utilize any of the eligible preventive services, with marginally significant indications of an increased risk in the intermediate categories.

Table 4-9. Unadjusted relative risks for advanced- versus early-stage laryngeal cancer at diagnosis.

	Laryngeal Cancer		
Usual Health Care Utilization Variables	**Unadjusted RR***	**(95% CI)**	***p*-value**
Number of health care encounters (*n* = 1,702)			
0 to 9 encounters	1.17	(1.00, 1.38)	0.0007
10 to 16 encounters	0.85	(0.69, 1.04)	
17 to 26 encounters	0.87	(0.71, 1.06)	
27 to 40 encounters	0.90	(0.74, 1.09)	
≥ 41 encounters	1.00	(Reference)	
Continuity of care (*n* = 1,508)			
High (UPC index ≥ 0.75)	1.00	(Reference)	0.04
Low (UPC index < 0.75)	1.18	(1.03, 1.35)	
Preventive services index (% of eligible services used) (*n* = 1,702)			
0%	1.70	(1.18, 2.33)	0.0005
> 0% and ≤ 50%	1.37	(0.95, 1.97)	
>50% and <100%	1.38	(0.94, 2.00)	
100%	1.00	(Reference)	

* Univariate log binomial regression

4.4.3.3 Model Selection

Four models for the effect of usual health care utilization on stage at diagnosis were fitted using all three utilization variables of interest, number of health care encounters only, continuity of care only, and preventive services use only. These models were adjusted for the five potential confounders identified previously. The adjusted relative risks (RRs) of advanced-stage laryngeal cancer was compared between models to determine whether it was necessary to model each utilization variable separately (see Table 4-10). In all four models, usual health care utilization was not associated with stage at diagnosis. The effect estimates varied by 3.7% to 9.5% between the model with the number of health care encounters only and the model adjusting for other utilization variables. Also, the adjusted relative risks for models with preventives services use only and continuity of care only differed by less than 2% versus the model with utilization measures together. Thus, the final analyses used the model with all three utilization variables since the effect estimates were stable across models.

Table 4-10. Adjusted relative risks for advanced- versus early-stage laryngeal cancer at diagnosis from models where usual health care utilization variables are included together or individually.

	Model 1† (*n* = 1,505)	Model 2† (*n* = 1,699)		Model 3† (*n* = 1,699)		Model 4† (*n* = 1,505)	
Usual Health Care Utilization Variables	**Adjusted RR* (95% CI)**	**Adjusted RR* (95% CI)**	**% Change**	**Adjusted RR* (95% CI)**	**% Change**	**Adjusted RR* (95% CI)**	**% Change**
Number of health care encounters							
0 to 9 encounters	0.88 (0.67, 1.15)	0.96 (0.75, 1.23)	9.5	----	----	----	----
10 to 16 encounters	0.80 (0.64, 1.02)	0.86 (0.69, 1.08)	7.1	----	----	----	----
17 to 26 encounters	0.82 (0.66, 1.02)	0.85 (0.69, 1.04)	3.7	----	----	----	----
27 to 40 encounters	0.88 (0.72, 1.06)	0.92 (0.77, 1.09)	4.9	----	----	----	----
≥ 41 encounters	1.00 (Reference)	1.00 (Reference)	----	----	----	----	----
Continuity of care							
High (UPC index ≥ 0.75)	1.00 (Reference)	----	----	----	----	1.00 (Reference)	----
Low (UPC index < 0.75)	1.02 (0.91, 1.15)	----	----	----	----	1.04 (0.93, 1.17)	1.9
Preventive services index (% of eligible services used)							
0%	1.30 (0.93, 1.80)	----	----	1.32 (0.96, 1.80)	1.8	----	----
> 0% and ≤ 50%	1.17 (0.85, 1.61)	----	----	1.16 (0.85, 1.58)	-0.3	----	----
>50% and <100%	1.15 (0.83, 1.60)	----	----	1.14 (0.83, 1.57)	-1.3	----	----
100%	1.00 (Reference)	----	----	1.00 (Reference)	----	----	----

* Log binomial regression adjusting for cancer subsite, age, sex, co-morbidity status, socioeconomic status, and health care utilization variables where applicable.

† Model 1: number of health care encounters + overall preventive services use + continuity of care; Model 2: number of health care encounters only; Model 3: overall preventive services use only; Model 4: continuity of care only.

4.4.3.4 Assessment of Confounding

From the multivariable log binomial regression analysis with the three measures of usual health care utilization together and adjustment for all potential confounders, a conventional backwards, stepwise approach was used to select the relevant confounders. Based on the statistical significance of the potential confounding variables with the risk of advanced-stage laryngeal cancer at diagnosis, only cancer subsite was retained in the model ($p < 0.0001$). Following this, the effect estimates for the utilization variables were compared between the final model and the fully adjusted model, in order to verify that all of the important confounding variables were included in the final regression analysis. The relative risk for advanced-stage laryngeal cancer comparing patients with 0 to 9 encounters versus those with ≥ 41 encounters changed by 14% between the two models. The relative risk for patients who used 0% of eligible preventive services compared to those who used 100% of eligible services differed by 47% between the two models, while there was a 2% change in the relative risk comparing low to high continuity of care. Due to the large variation in effect estimates for two of the utilization measures, co-morbidity status was added back to the model to reduce confounding bias. This reduced the changes in the effect estimates to less than 10%. Therefore, both laryngeal cancer subsite and co-morbidity status affected the associations between the usual health care utilization measures and stage at diagnosis.

4.4.3.5 Final Models

The results of the adjusted log binomial regression model for all laryngeal cancer patients showed that supraglottic cancer patients were substantially more likely to be diagnosed with advanced-stage disease compared to those with glottic cancer (RR [95% CI]: 3.18 [2.80, 3.61]). It was hypothesized, *a priori*, that laryngeal cancer subsite was an effect modifier of the relationship between usual health care utilization and stage at diagnosis. Preliminary stratified analyses for the unadjusted associations between usual health care use and stage at diagnosis showed that the effect of the frequency of health care visits, in particular, was quite different for glottic and supraglottic cancer patients (see Figure 4-4). Thus, the final adjusted analyses were conducted separately for glottic cancer and supraglottic cancer patients to examine effect modification.

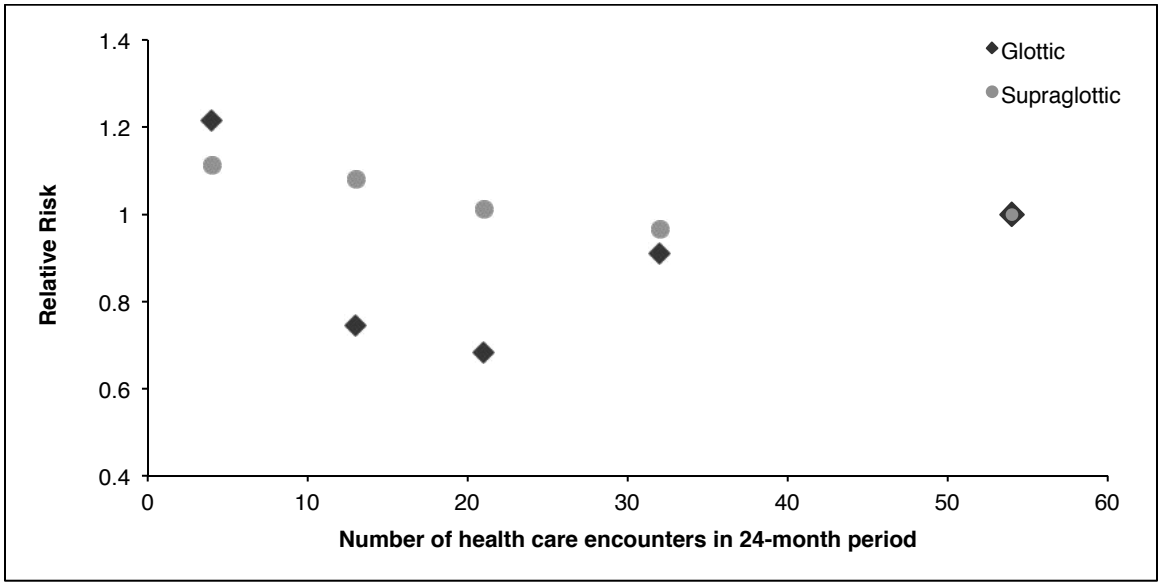

Figure 4-4. Unadjusted relative risks for advanced- versus early-stage laryngeal cancer for the number of health care encounters, stratified by subsite, where the highest quintile was the reference category.

Table 4-11 presents the multivariable log binomial regression analyses for usual health care utilization and the likelihood of advanced-stage diagnosis, stratified by laryngeal cancer subsite. For glottic and supraglottic cancer patients, there was no evidence to show that patients who had fewer health care encounters had an increased risk of advanced-stage disease, which was the hypothesized association. In fact, the effect estimates indicated an opposite trend in the glottic cancer patients where those who had a moderate number of health care visits during a two-year period had a lower risk of advanced-stage disease compared to those who used the most health care (RR [95% CI]: 0.67 [0.45, 0.99]). Having low continuity of care with a GP/FP was marginally associated with a higher risk of being diagnosed with advanced disease among glottic cancer patients (RR [95% CI]: 1.25 [0.98, 1.58]). The association between continuity of care and stage at diagnosis was weaker when subsites were combined, but the association was statistically significant. Although not statistically significant, the effect estimates indicated that laryngeal cancer patients who did not use any eligible preventive services might have been more likely to be diagnosed with advanced-stage disease than those who accessed all preventive services. This finding was similar for glottic and supraglottic cancer and was significant when subsites were combined (RR [95% CI]: 1.50 [1.04, 2.18]). Overall, the differences in the relative risk estimates between the glottic and supraglottic cancer strata support effect modification by subsite. Specifically, the effect estimates indicated a decreased risk of advanced stage with fewer health care encounters and an increased risk with low continuity of care in glottic cancer, while the effects were null in supraglottic cancer. Additionally, there was evidence of confounding by subsite because the relative risk estimates for overall preventive services use were much stronger when all laryngeal cancer was considered versus glottic or supraglottic cancer only.

Table 4-11. Adjusted relative risks for advanced- versus early-stage laryngeal cancer at diagnosis, stratified by subsite.

Usual Health Care Utilization Variables	Laryngeal Cancer (*n* = 1,508)	Glottic Cancer (*n* = 1,073)		Supraglottic Cancer (*n* = 435)	
	Adjusted RR* (95% CI)	Adjusted RR* (95% CI)	*p*-value	Adjusted OR* (95% CI)	*p*-value
Number of health care encounters					
0 to 9 encounters	0.99 (0.74, 1.32)	0.87 (0.54, 1.40)	0.19	0.94 (0.68, 1.29)	0.92
10 to 16 encounters	0.80 (0.61, 1.05)	0.66 (0.43, 1.02)		0.97 (0.72, 1.30)	
17 to 26 encounters	0.87 (0.69, 1.10)	0.67 (0.45, 0.99)		0.92 (0.71, 1.19)	
27 to 40 encounters	0.89 (0.72, 1.09)	0.88 (0.63, 1.23)		0.91 (0.72, 1.15)	
≥ 41 encounters	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	
Continuity of care					
High (UPC index ≥ 0.75)	1.00 (Reference)	1.00 (Reference)	0.07	1.00 (Reference)	0.89
Low (UPC index < 0.75)	1.17 (1.01, 1.34)	1.25 (0.98, 1.58)		1.01 (0.89, 1.15)	
Preventive services index (% of eligible services used)					
0%	1.50 (1.04, 2.18)	1.27 (0.76, 2.13)	0.63	1.29 (0.84, 1.97)	0.43
> 0% and ≤ 50%	1.35 (0.93, 1.94)	1.08 (0.65, 1.79)		1.18 (0.77, 1.80)	
>50% and <100%	1.38 (0.95, 2.00)	1.09 (0.64, 1.84)		1.17 (0.76, 1.80)	
100%	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	

* Log binomial regression, adjusted for co-morbidity status and all other health care utilization variables in the table.

4.4.3.6 Sensitivity Analysis

The median length of time between diagnosis of laryngeal cancer and registration at a regional cancer centre was 16 days (IQR: 18 days). There was concern that the stage recorded for patients who registered later in the disease course may be more advanced than at diagnosis. The distributions of early- and advanced-stage cancer were examined for patients whose RCC registration date was more than 30, 60, and 90 days from their date of diagnosis to determine if stage assignment was related to the time of registration. These results are presented in Table 4-12 for glottic and supraglottic cancer. For both types of laryngeal cancer, the distributions of stage at diagnosis for patients who registered at a RCC within 60 days or 90 days were similar to those who registered after those time intervals. Similarly, for the comparison at the 30-day interval, there was no variation in the proportion of patients with advanced-stage supraglottic cancer. However, for glottic cancer, more early-staged patients were among the group who took longer than 30 days to register at a RCC compared to those who were seen at a cancer centre within a 30-day period. This finding is consistent with what occurs in the clinical setting because patients may have a biopsy that was also for treatment and have a recurrence, pathological confirmation may take more time with small tumour samples, or a second biopsy is required for confirmation. This finding did not warrant a separate analysis among the glottic cancer patients who registered within 30 days, as it does not constitute evidence that the disease stage recorded misrepresented stage at diagnosis. Thus, the planned sensitivity analyses to assess the effects of issues with initial stage assignment at diagnosis were not needed.

Table 4-12. Proportion of early- and advanced-stage glottic and supraglottic cancer for patients who registered at a RCC before or after 30, 60, and 90 days from diagnosis.

Duration from diagnosis to RCC Registration	Glottic Cancer (*n* = 1,073)			Supraglottic Cancer (*n* = 435)		
	Stage I/II	Stage III/IV	*p*-value*	Stage I/II	Stage III/IV	*p*-value*
0 to 30 days (*n* = 957)	73.98	26.02	0.003	25.88	74.12	0.88
> 30 days (*n* = 248)	83.06	16.94		25.00	75.00	
0 to 60 days (*n* = 1,128)	75.62	24.38	0.48	25.79	74.21	0.94
> 60 days (*n* = 77)	79.22	20.78		25.00	75.00	
0 to 90 days (*n* = 1,151)	75.67	24.33	0.51	25.88	74.12	0.71
> 90 days (*n* = 54)	79.63	20.37		21.43	78.57	

* Chi-square test of independence.

4.5 Regression Diagnostics

For each of the final adjusted models, collinearity diagnostic statistics and regression diagnostic statistics were examined. In the multivariable analyses, the independence of the usual health care utilization variables was demonstrated in model selection because the effect estimates were not significantly different between the models with variables together and the models with each health utilization variable separately. Collinearity diagnostic statistics, including variance inflation factors, condition numbers, and variance proportions, were also used to assess independence among the predictor variables. The variance inflation factors from the final models for Objective 1 and Objective 2 were less than seven. In addition, the largest condition numbers for the regression analyses modelling the probability of Stage III or IV laryngeal cancer, Stage III or IV glottic cancer, and Stage III or IV supraglottic cancer were 5.8, 4.9, 4.7, and 6.3, respectively, which is significantly less than the cut-off of 30. Although there were two or more variance proportions greater than 50% loading on the corresponding eigenvalues, these were for dummy variables. Therefore, considering these three diagnostics, collinearity among independent variables was not a problem for any of the models.

To assess the fit of the three adjusted models, the residual, leverage, and influence of observations were checked. Analysis of these regression diagnostic statistics did not identify any strongly influential observations, since all of the predictor variables were categorical. In addition, the Hosmer-Lemeshow goodness-of-fit test was performed for the log binomial regression models. For the multivariate analyses of glottic cancer and supraglottic cancer, the test yielded *p*-values of 0.67 and 0.28, respectively. These test results also supported the fit of the models. Overall, the conditional logistic and log binomial models fit the data and no observations had to be excluded from the analyses.

CHAPTER 5 DISCUSSION

5.1 Summary of Study

The current study was conducted to elucidate patterns of usual health care utilization among patients diagnosed with laryngeal cancer. The preliminary objective was to compare usual health care utilization between laryngeal cancer patients and the general population to provide context for patients' health care use. The main objective of the study was to assess the associations between usual health care utilization before diagnosis and stage at diagnosis among laryngeal cancer patients. These study objectives were investigated using a matched case-control study design and a retrospective cohort study design, respectively. Linked demographic, clinical, and health administrative data, from the Institute for Clinical Evaluative Sciences in Ontario, were used to identify the study population, characterize usual health care utilization, assess stage at diagnosis, and collect information on a number of important demographic and clinical covariates. Conditional logistic regression and log binomial regression were conducted to examine the two objectives of the study.

5.2 Key Findings

5.2.1 Comparison of Usual Health Care Utilization between Laryngeal Cancer Patients and the General Population

This population-based study showed that there is a difference between laryngeal cancer patients' and the general population's utilization of health care. Since use of health services is determined by an individual's health status and other demographic characteristics (22), it was important to adjust for a number of these factors in the study's design and analyses. Matching laryngeal cancer patients and the general population on age, sex, and area of residence ensured that the distributions of these factors, as well as rurality and

socioeconomic status (both ecologic variables) were comparable between the two groups. Moreover, Canada has a universal, publicly funded health care system, which reduced disparities in access to health care. Further statistical adjustment for co-morbidity status was necessary because the degree of co-morbid illness was significantly associated with laryngeal cancer status.

After controlling for factors that could explain variations in health care utilization, the study found that the frequency of health care encounters during a two-year period and the overall use of preventive health services were associated with laryngeal cancer status. In comparison to the general population, laryngeal cancer patients were more likely to have fewer health care encounters in a two-year period and use more eligible preventive services. Primary care model enrolment status and continuity of care with a general practitioner were similar for individuals diagnosed with laryngeal cancer and those without the disease. Provider and system factors, rather than individual characteristics may influence these two measures of health care utilization. As such, matching laryngeal cancer patients and the general population by subLHIN may have reduced much of the variation in the characteristics of the health care provider and system. However, the differences in the number of health care visits and use of preventive health care suggest that there are other characteristics of laryngeal cancer patients, besides the demographic and clinical characteristics considered, that influence their usual use of health services.

Previous research has not described health care utilization among patients with laryngeal cancer in detail nor made comparisons to the general population. In the current study, laryngeal cancer patients were more likely than the general population to have fewer visits to physician offices, emergency departments, and hospitalizations in a two-year period. A possible explanation for this finding is that individuals diagnosed with laryngeal cancer have different health behaviours and beliefs than the general population. The laryngeal

cancer patient population is often engaged in health-risk behaviours, such as smoking and excessive alcohol consumption. Tromp et al. (121) have shown that these health-risk behaviours are associated with lower levels of health value and perceived health competence among head and neck cancer patients. Therefore, laryngeal cancer patients may use health care less frequently than the general population because they place less importance on their health and do not believe that their behaviours, such as seeking help from health care professionals, can improve their health.

Surprisingly, patients with laryngeal cancer also had a greater propensity for utilizing the preventive health care recommended for their age and sex. Compared to the general population, laryngeal cancer patients were more likely to use at least half of the eligible preventive services. Although the association was weak, this finding appears to counter the hypothesis that laryngeal cancer patients have poor health behaviours, which affect health care utilization. A possible explanation for this finding is that laryngeal cancer patients who decide to seek preventive services are more likely than those in the general population to utilize other preventive health care. The propensity for accessing additional preventive health care may be driven by an individual's annual physical examination, where physicians will often initiate the process for patients to receive recommended cancer screening. The study results suggest that this group of laryngeal cancer patients are females because the rates of breast and cervical cancer screening were significantly higher compared to the rates for general population. Thus, the gender differences regarding health values that have been reported in the literature (122) are also apparent among laryngeal cancer patients. Female laryngeal cancer patients appear to value their health more than males, and this health belief is reflected in their use of preventive services.

5.2.2 Association between Usual Health Care Utilization and Stage at Diagnosis among Laryngeal Cancer Patients

Overall, the current study did not find convincing evidence for an association between usual health care utilization before diagnosis and stage at diagnosis in laryngeal cancer, after controlling for patients' co-morbidity status. However, the results suggest that the effect of usual health care use on the risk of advanced-stage disease varies between the two subsites of laryngeal cancer. An explanation for effect modification by subsite is the symptom presentations of the diseases, particularly the point in disease progression at which symptoms become apparent. Stage at diagnosis in supraglottic cancer may be driven by the late presentation of symptoms, which limits the effects of usual health care utilization. The differential effect by subsite may also reflect the different risk factors of glottic and supraglottic cancer. While both glottic and supraglottic cancers are caused by smoking, alcohol consumption is an important etiologic factor for supraglottic cancer as well. The heavy drinking of supraglottic cancer patients may indicate other poor health behaviours that distinguish them from glottic cancer patients. Since heavy drinking is generally associated with less health care use (123), the lack of variation may explain the results in supraglottic cancer. For patients diagnosed with supraglottic cancer, neither frequency of health care encounters, nor continuity of care were associated with having advanced-stage cancer at diagnosis. Among glottic cancer patients, the current study found marginal associations for the number of health care visits and continuity of care with the risk of being diagnosed with advanced-stage cancer. For glottic and supraglottic cancer patients combined, use of eligible preventive services was negatively associated with the risk of an advanced-stage diagnosis. However, this association was not evident when stratified by subsite.

A few studies have examined the relationship between the frequency of health care visits and stage of laryngeal cancer at diagnosis. In the current study, the median number of

health care encounters in a two-year period was significantly lower for patients with late-stage laryngeal cancer compared to those with early-stage cancer (19 versus 21 encounters; $p = 0.02$). A significant difference was also reported by Prout et al. (45) in their study of head and neck cancer patients. Interestingly, the results of the current study showed that having fewer health care encounters before diagnosis was marginally associated with a reduced risk of advanced-stage glottic cancer. The risk of advanced glottic cancer was about 33% less for those who had 10 to 26 encounters in the two years before diagnosis compared to those who had more than 41 encounters (RR [95% CI]: 10 to 16 visits, 0.66 [0.43, 1.02]; 17 to 26 visits, 0.67 [0.45, 0.99]). This finding contrasts with those by Reid et al. (8) who reported that laryngeal cancer patients who had six or more physician visits one year prior to diagnosis were between 51% and 79% less likely than those with zero visits to be diagnosed with advanced-stage disease ($p \leq 0.05$). The difference in results may be attributed to the choice of reference group in the studies. Laryngeal cancer patients who do not use any health care may be a distinct population who engage in a variety of health-risk behaviours and do not evaluate their health needs and seek help accordingly. Additionally, there may be other factors that affect these patients' ability to access health services when needed. Therefore, comparing health care users to a group of non-users may overestimate the association between the number of health care visits and stage at diagnosis. Furthermore, Reid et al. (8) did not exclude physician visits in the period directly preceding diagnosis, which could also bias the results away from the null. However, the direction of the current study's results were surprising because it was hypothesized that patients with fewer encounters would have an increased risk of advanced-stage laryngeal cancer. A decreased risk of an advanced-stage diagnosis was only found for patients who had 10 to 26 encounters in a two-year period, which suggests that regular health care contacts (i.e. a visit every one to two months) by glottic cancer patients is important for earlier diagnosis of the disease. On the other hand,

having more frequent health care encounters does not appear to be protective of advanced-stage disease at diagnosis. More encounters may be indicative of more co-morbidities, which might detract attention from the earlier symptoms of glottic cancer.

The current study also showed evidence of an inverse association between the continuity of care and stage at diagnosis for patients with glottic cancer, which was consistent with the results of the research by Reid and colleagues (26). Reid et al. (26) reported a 19% increase in the likelihood of advanced laryngeal cancer at diagnosis for patients who had low continuity of care with an internist (OR [95% CI]: 0.84 [0.69, 1.02]), while there was a weaker association for continuity of care with a GP/FP (OR [95% CI]: 0.92 [0.74, 1.15]). Similarly, the current study found that glottic cancer patients who had low continuity of care with a GP/FP were 1.25 times more likely to be diagnosed with advanced-stage disease than those with high continuity of care (RR [95% CI]: 1.25 [0.98,1.58]). Although the effect of continuity of care on the risk of advanced glottic cancer was borderline statistically significant, the direction of the relationship indicates that having a regular physician improves the chance of an earlier diagnosis. A potential explanation is that the physician is familiar with their patient's smoking and drinking behaviours and may be more likely to suspect laryngeal cancer when he or she present with hoarseness. In addition, patients with a regular physician may have a greater tendency to seek care when symptoms present. Therefore, having high continuity of care with a physician can increase the opportunities for early detection and diagnosis of laryngeal cancer.

The association between preventive services use and stage at diagnosis has not been examined for laryngeal cancer previously. The current study found evidence of an association between laryngeal cancer patients' propensity for using preventive health care and the risk of advanced-stage cancer. Patients who did not use any preventive services were 1.50 times more likely to have advanced-stage laryngeal cancer than those who used all

eligible preventive services (RR [95% CI]: 1.50 [1.04, 2.16]). Weaker, non-significant effect estimates were found after stratifying into glottic cancer (RR [95% CI]: 1.27 [0.76, 2.13]) and supraglottic cancer (RR [95% CI]: 1.29 [0.84, 1.97]). However, the direction of the associations in the current study indicates that patients who use less preventive health care have an increased risk of being diagnosed with advanced-stage laryngeal cancer. A previous study by Gornick et al. (59) found that using two or more preventive services was associated with a reduced likelihood of late-stage breast, colorectal, prostate, uterine, and bladder cancers, but there was no association for ovarian and stomach cancers. Based on the work by Gornick et al. (59) and the findings from the current study, preventive health care use appears to be an indicator of other positive health behaviours, such as seeking care for signs and symptoms of cancer.

5.3 Methodological Considerations

5.3.1 Study Design

One of the strengths of the study is that it utilized electronic, provincial databases. Collecting data on usual health care utilization, demographics, and clinical characteristics from the electronic databases eliminated any potential for recall bias. Another strength of the current study is that it was population-based. The selected study period ensured that all laryngeal cancer patients seen at Ontario's Regional Cancer Centres could be captured. This is important because staging data for diagnoses before this period were not available for Princess Margaret Hospital, which is the largest RCC in Ontario and represents over one-third of cases. Although a proportion of eligible laryngeal cancer patients were excluded from the study due to missing data, the comparison of demographic and clinical characteristics showed that the age and sex distributions were similar between those included or excluded from the study. The distributions of laryngeal cancer subsite and LHIN of

residence were statistically different, but the findings do not suggest a systematic reason for patients being excluded from the study population (see Section 4.2.1). Also, the distribution of early- and advanced-stage disease in the current study's laryngeal cancer cohort was comparable to the distributions reported previously for the Ontario population (6) and for the United States' Surveillance, Epidemiology and End Results (SEER) program (124) (see Table 5-1). Therefore, the study population is representative of all laryngeal cancer patients across the province of Ontario and selection bias was not a concern.

The comparison cohort was identified from the Registered Persons Database, which is a population-based registry of all individuals who have been covered by OHIP. However, there are some issues concerning the matching strategy used to select the comparison cohort. Since the comparison cohort was matched to the laryngeal cancer cohort by age, sex, and subLHIN, the comparison cohort may be too similar to the laryngeal cancer cohort, thus biasing those comparisons toward the null. In particular, matching by subLHIN resulted in a comparison cohort with similar area-level socioeconomic status and therefore, potentially similar use of health services. Lastly, matching by sex eliminated the ability to examine the relationship between sex and laryngeal cancer status, and assess whether sex modified the study's results.

Table 5-1. Comparison of laryngeal cancer stage distribution.

Stage	Laryngeal Cancer Cohort	Ontario 1985–1997 (6)	SEER 2001–2007 (124)
Early (Stage I/II or Localized)	61%	65%	57%
Advanced (Stage III/IV or Regional/Distant)	39%	34%	37%

5.3.2 Exposure Assessment

In the current study, four components of health care utilization were considered for the exposure assessment. This improves upon previous research on health care utilization among patients with laryngeal cancer, which have only examined the number of encounters

and continuity of care individually. Examining the frequency of health care visits, continuity of care, enrolment in a primary care model, and use of preventive services allowed the study to understand which specific aspects of health care use are important determinants of having laryngeal cancer or being diagnosed with advanced-stage disease. As mentioned previously, these measures of health care utilization could be ascertained, without recall bias, from the electronic databases. All of the ambulatory care, hospitalizations, and preventive services considered in the current study are covered by the Ontario Health Insurance Plan, so this information is available from the OHIP claims database or the CIHI-DAD. Although the study population had OHIP coverage during the three years prior to the study index date, it is possible for individuals to have received health care outside of Ontario, which would not be captured in the study data sources. This is because individuals are eligible for OHIP coverage if they reside in Ontario for a minimum of 153 days in a year (125). This may have resulted in an underestimate of usual health care utilization, but the number of individuals in the study who fall into this category is probably small.

There are some issues related to the data sources used to measure usual health care utilization that need to be addressed. Firstly, the completeness of the OHIP claims database is a potential concern because health care utilization data may be incomplete for a proportion of the study population. As explained previously, claims may be underreported in four LHINs due to a significant number of physicians being compensated through an alternate funding plan. The analysis of the distribution of health care encounters showed that among the laryngeal cancer cohort the median number of visits was not different for patients in the AFP LHINs compared to the other LHINs, but there was a difference among the comparison cohort (see Section 4.2.2). Matching the laryngeal cancer cohort and the comparison cohort on subLHIN likely controlled for this difference in the analyses for Objective 1. However, if undocumented health care encounters were more prevalent for individuals from the non-AFP

LHINs, this missing data would be present for the laryngeal cancer cohort, comparison cohort, patients with early-stage disease, and patients with advanced-stage disease (i.e. non-differential misclassification). Thus, these missing health care encounters would mean that the associations of interest were underestimated in the current study.

The study's measure of preventive health care use considered five health services that are recommended for individuals aged 40 years and older. This was a strength of the study because the preventive services index provided a more comprehensive measure of individuals' propensity for using preventive health care and was a proxy for health behaviours. Additionally, the preventive services index accounted for an individual's eligibility for each preventive service based on age and sex. However, this measure of preventive services use is dependent on the accuracy of assessing use of each preventive service.

Preventive services use was primarily determined from the OHIP claims database, based on algorithms that have been used in previous research. Assessment of influenza vaccination status using health administrative data only tends to underestimate usage. This is attributed to the fact that approximately one-third of the population are vaccinated at public health clinics or the workplace, which is not captured by the OHIP claims data (67). However, the rate of influenza vaccination in the general population study group was within the self-reported rate of vaccination for individuals 50 years or older (52% versus 47–75%) (67). For the assessment of cancer screening status, the study was not able to distinguish between tests used for screening or diagnostic purposes due to the limitations of using health administrative data. Twenty-three percent of the study's general population had colorectal cancer screening. This was consistent with the rate of colorectal cancer screening in the eligible Ontario population (17% for 2002-2004) (56), which continued to increase throughout the decade. However, the rates of breast and cervical cancer screening in the study's general population were lower than the rates reported for eligible women in Ontario

(mammography: 45% versus 66%; Pap test: 39% versus 68–73%) (64,65). Since the differences were observed for female cancer screening tests only, it suggests that the women in the study's general population are not representative of all Ontario women with regard to their screening behaviours. Matching by age and subLHIN to female laryngeal cancer patients may have resulted in more women with low socioeconomic status and rural residence, which are factors that contribute to lower use of screening.

5.3.3 Outcome Assessment

The outcome, stage at diagnosis, was assessed using clinical and pathological TNM classifications from Cancer Care Ontario data. A limitation of the staging data used in the current study is that stage was only recorded at Regional Cancer Centres. Thus, the documented stage may not represent the initial stage at the time of diagnosis and could be upstaged because of length of time from diagnosis to treatment at a RCC. This source of measurement bias would be non-differential and result in a weaker estimate of the association between usual health care use and stage at diagnosis. However, the findings from the sensitivity analysis suggest that this is not a concern because the proportion of advanced-stage laryngeal cancer patients was not increased among those who had a long delay between diagnosis and RCC registration.

Both clinical and pathological stage groups were used to maximize the number of laryngeal cancer patients included in the study. These stage groups were either derived from TNM classifications or were recorded by physicians. There was strong agreement between stage groups determined from these two methods (clinical staging: kappa = 0.98; pathological staging: kappa = 0.97). However, the use of both clinical and pathological staging introduced the possibility of stage migration, which may affect the accuracy of the outcome measurement.

In the current study, stage at diagnosis was dichotomized as early-stage (Stage I or II) and advanced-stage (Stage III or IV) laryngeal cancer in the multivariable analyses, so migration between T2 and T3 disease could have resulted in misclassification of the outcome. A distinguishing characteristic between T2 and T3 laryngeal cancer is vocal cord fixation. This, however, is a relatively stable clinical finding and its detection does not change significantly with additional imaging or surgical procedures (3). The degree of invasion by laryngeal tumours also differentiates T2 and T3 disease, which can be affected by the imaging technology used to stage the cancer. Previous research on staging in laryngeal cancer demonstrated that the use of computed tomography (CT) or magnetic resonance imaging (MRI), in addition to a clinical examination, improves accuracy and results in upstaging of the tumour in approximately 20% of cases (6,126). For patients without CT or MRI, clinical stage may be underestimated compared to clinical staging with imaging tests or pathological staging. Therefore, misclassification of laryngeal cancer patients with advanced-stage disease to early-stage disease would cause the association of interest to be biased towards the null because measurement bias occurred among the exposed and unexposed patients. However, during the study period, CT or MRI was likely used to determine clinical stage for the majority of laryngeal cancer patients.

5.3.4 Covariate Assessment

Another strength of the current study was the consideration of a number of potential confounders, in order to obtain a true estimate of the effect of usual health care utilization on stage at diagnosis of laryngeal cancer. Covariates were selected *a priori* based on evidence showing associations with the exposure and outcome of interest. A particular strength of the analyses was that a conventional backward selection method and a change-in-estimate

approach were used. This helped ensure that all of the important confounders of the association of interest were accounted for in the analyses.

It is also important to discuss the measurement of the covariates. Using electronic databases, information on the demographic characteristics could be determined quite accurately and completely for the study population. The measure of co-morbidity status used in the current study was developed for research using administrative health databases. It is worth noting that this characteristic of the measure means that co-morbidity status is dependent on individuals seeking health care for their illnesses. The regression diagnostics did not indicate a problem of collinearity between co-morbidity status and the number of health care encounters. However, bivariate analyses using chi-square tests showed that the study's measure of co-morbidity status was associated with the frequency of health care visits ($p < 0.0001$). If these measures are highly correlated, adjusting for co-morbidity status in the multivariable analyses may have biased the effect estimates towards the null.

Another limitation to using electronic databases for data collection was that information on tumour biology could not be ascertained. As such, the study was unable to account for the aggressiveness of laryngeal tumours (i.e. how quickly it progresses to advanced-stage disease) in the analysis and the potential effects on the association between usual health care utilization and stage at diagnosis. However, the current study conducted stratified analyses by laryngeal cancer subsite, which may have accounted for some of the effect of tumour biology on disease progression. Another covariate that could not be assessed using electronic health administrative databases is race. This is an important variable to consider in the study, because race is associated with usual health care utilization (23) and stage at diagnosis of laryngeal cancer (24,26). Consequently, the study results for the association between usual health care use and stage at diagnosis may be partially explained by residual confounding due to race.

5.3.5 Statistical Analyses

In the current study, log binomial regression was used to examine the association between usual health care utilization and stage at diagnosis of laryngeal cancer. An advantage of this regression technique is that it allowed for the relative risk to be estimated and for adjustment of confounding factors. For this analysis, the outcome was dichotomized as Stage I or II and Stage III or IV disease because these are the clinical classifications used to define early- and advanced-stage disease. The bivariate analyses showed that the largest differences in usual health care utilization were between laryngeal cancer patients diagnosed with Stage I and Stage IV disease (see Table 4-8). However, multivariable log binomial regression models with and without adjustment for confounding did not show a statistically significant association between the usual health care utilization variables and the risk of advanced-stage laryngeal cancer (see Table 4-10 and Table 4-11). This suggests that combining the stage groups may have reduced the ability to detect differences in health care utilization across the stage groups. Thus, to gain a better understanding of the effect of usual health care utilization on stage at diagnosis, it will be important to consider the four stage groups in future regression analyses of these data.

5.3.6 Sample Size

For the thesis proposal, minimum detectable differences for a comparison of selected health care utilization variables between patients with early- and advanced-stage laryngeal cancer were calculated. The detectable differences were estimated to achieve 80% power and a two-sided significance level of 0.05. The *a priori* calculations were based on sample size of 1,262 laryngeal cancer patients and health care utilization data that were available for oral cavity cancer patients (details for these calculations are in Table C-1 in Appendix C). However, the final size of the laryngeal cancer cohort was 1,702 and health care utilization

for laryngeal cancer patients was different than the oral cavity population. Since the sample size was much larger than estimated, the study was actually powered to detect smaller differences. Thus, the study had sufficient power to detect an association between usual health care utilization and stage at diagnosis if one truly existed.

The relatively large sample size of the study enabled the association between usual health care utilization and stage at diagnosis to be assessed separately for patients with glottic and supraglottic cancers. This is a particular strength of the study because previous research has examined this relationship for all subsites of laryngeal cancer or in combination with other head and neck cancers. However, it is known that the symptom presentation for glottic and supraglottic cancers differ and may explain stage at diagnosis, which is why consideration of potential effect modification by subsite was crucial for understanding the effect of health care use on stage of laryngeal cancer at diagnosis. The current study met the criteria of ten events (i.e. Stage III or IV laryngeal cancer) per variable for regression analyses, recommended by Peduzzi and colleagues (127). The final log binomial models had 12 variables each, while there were 242 and 316 cases of advanced-stage glottic and supraglottic cancer, respectively. Therefore, the study had a sufficient number of events per variable to maintain the validity of the regression models examining the relationship between usual health care utilization and stage at diagnosis.

5.3.7 Generalizability

A few limitations of the current study were identified, but these are mostly minor and do not threaten the validity of the study. In addition, this is a population-based study that is not affected by selection bias. Therefore, it is reasonable to suggest that the study's findings on the associations between usual health care utilization and stage at diagnosis can be generalized to other laryngeal cancer patients who have access to health services that is

comparable to the study population. Access to health care, particularly health insurance status, is necessary to consider with respect to the study's external validity because these factors have a significant effect on an individual's basic use of health care. With this in mind, the findings from the current study are likely generalizable to laryngeal cancer patient populations from other Canadian provinces, where residents are also covered by the provincial health insurance plans. Furthermore, since the majority of laryngeal cancers are diagnosed among individuals aged 40 years and older, findings of the current study may not be representative of the effects present in younger patient populations.

5.4 Conclusions

The current study provides valuable information on patterns of usual health care utilization among laryngeal cancer patients, which has not previously been examined within the Canadian experience. Findings from the current study showed that patients who are diagnosed with laryngeal cancer use health care differently than the general population. Most notably, laryngeal cancer patients had significantly fewer health care visits than the general population. Reduced contact with health care professionals limits the opportunities for health promotion, specifically related to the health risks associated with excessive smoking and alcohol consumption. However, the greater use of preventive health services among laryngeal cancer patients suggests that there are also missed opportunities for educating high-risk individuals about the risk factors, signs, and symptoms of laryngeal cancer. Since no previous studies have compared usual health care utilization between laryngeal cancer population and the general population, further research is needed to confirm these relationships. Furthermore, the current study controlled for important determinants of health care use, including demographic characteristics and co-morbid illness, but investigating

health beliefs of laryngeal cancer patients may be useful for understanding this population's use of health care.

Given the significant proportion of advanced-stage diagnoses in laryngeal cancer, it is important to understand the characteristics and behaviours of this population that contribute to this process. This knowledge is invaluable towards increasing early detection and diagnosis of laryngeal cancer. The current study contributes to the limited literature that has examined the relationship between laryngeal cancer patients' usual health care utilization and the risk of advanced-stage at diagnosis. Findings from the current study did not confirm the association between the number of health care visits and stage previously observed. Rather, the current study suggests that regular health care contacts reduce the risk of being diagnosed with advanced-stage glottic cancer. The marginal association found in the current study and a previous study also suggests that high continuity of care may be important for reducing the risk of being diagnosed with advanced-stage laryngeal cancer.

This is only the fourth study to have examined the association between health care utilization and stage at diagnosis of laryngeal cancer. As such, further research is needed to confirm whether an individual's pattern of usual health care utilization predicts advanced diagnosis of laryngeal cancer. In particular, it is important to elucidate the variations in health care use among patients across the four stages of laryngeal cancer. Future analyses on these data using the polytomous logistic model or the proportional odds model will help examine the specific associations for the each stage of laryngeal cancer. Consideration of the type of health care provider, such as primary care providers versus specialists, may also provide additional insight into this relationship. This is because physician awareness of laryngeal cancer may differ among health care providers and affect diagnosis.

In summary, laryngeal cancer patients' patterns of usual health care use may limit the opportunities for health care providers to educate these individuals about the disease and

monitor any changes in health. Therefore, in order to increase early detection and diagnosis, it may be most effective to target high-risk individuals with interventions aimed at informing about the signs and symptoms of laryngeal cancer outside of the health care setting. Strategies for early detection and diagnosis should also aim to increase awareness about laryngeal cancer among health care providers, particularly family physicians. Specifically, knowledge of the risk factors, signs, and symptoms of the disease, will help providers diagnose laryngeal cancers in a timely manner. For these interventions to be effective, an important first step will be to characterize the individuals who are at high risk for being diagnosed with advanced laryngeal cancer.

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APPENDIX A DATASET CREATION PLAN

Cohort Dataset Creation Plan	
Name and Number of Study	The association between usual health care utilization and stage at diagnosis in laryngeal cancer (Project # 2011 0800 128 000)
Contacts	Felicia Leung, Patti Groome
Who will be responsible for DCP updates?	Felicia Leung
PIA Approved?	Approved
DCP update history	Created: April 2011 Last Updated: August 19, 2011

Short Description of Research Question

Early diagnosis of laryngeal cancer is key for good prognosis. However, many individuals are diagnosed at an advanced stage even though it is easily detectable in clinical examinations. Current research examining variations in stage at diagnosis for laryngeal cancer is limited. This study will address gaps in the literature by examining the relationship between usual health care utilization prior to diagnosis within the Canadian context. This will enhance our understanding of the processes that contribute to late diagnosis in laryngeal cancer and will help identify opportunities in the health care system to improve early detection of the disease. The study objectives are:

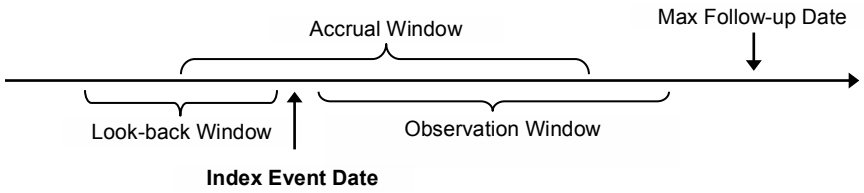
1. To contextualize usual health care utilization among laryngeal cancer patients through a comparison to a frequency-matched cohort of the general population in Ontario.
2. To evaluate the associations between stage at diagnosis and usual health care utilization (frequency, type, and continuity) prior to diagnosis in a cohort of laryngeal cancer patients in Ontario.

List of Datasets Used	CCE Stage File, OCR, OBSP, OHIP, CIHI-DAD, CAPE, IPDB, RPDB, PSTLYEAR, PCCFyyyy

Defining the Cohort	
Index Event	**1. Laryngeal Cancer Cohort:** Diagnosis of single, primary, squamous cell carcinoma of the glottis or supraglottis between January 1, 2002 and December 31, 2008 for patients aged 40 or older who have OHIP coverage during the 39 months before diagnosis. i. From OCR and CCE Stage File data: - *dxdate* = 'between Jan. 1, 2002 and Dec. 31, 2008' - *age ≥ 40* - *dxcode = 161.0 or 161.1* (ICD-9 codes) - *hist = 8050, 8052 to 8084* (ICD-O-3 histology codes) - *prim = 01* (single, primary cancer) ii. Create a dataset for all laryngeal cancers meeting the above criteria - Include *age, sex, dxdate, dxcode, hist, lhin* **2. Comparison Cohort:** Residents of Ontario aged 40 or older who have OHIP coverage during the 39 months before the index date and do not have a previous diagnosis of cancer. i. Individual-matching with laryngeal cancer cohort by birth year (5-year intervals), sex, and subLHIN - Use %getdemo macro to get *byear, sex, sublhin* ii. Assign index date to each individual in the comparison cohort that corresponds to the data of diagnosis for the matched individual in the laryngeal cancer cohort
Exclusions (In order)	**Laryngeal Cancer Cohort:** i. Not registered at a Regional Cancer Centre (i.e. not in CCE Stage File) ii. Stage group cannot be defined

Size of Cohort	**1. Laryngeal Cancer Cohort:** 1,702 **2. Comparison Cohort:** 8,510

Time Frame Definitions



Accrual Start/End Dates	January 1, 2002 – December 31, 2008
Max Follow-up Date	N/A (retrospective cohort study)
When does observation window terminate?	Date of laryngeal cancer diagnosis or index (index event = outcome)
Lookback Window(s)	**1. Laryngeal Cancer Cohort:** 3 to 27 months before the date of the laryngeal cancer diagnosis (i.e. 2-year period) **2. Comparison Cohort:** 3 to 27 months before the index date (i.e. 2-year period) *Note: Longer look back windows for cancer screening variables*

Variable Definitions

Main Exposure or Risk Factor

1. Number of health care encounters in <u>3 to 27 months</u> before index event

Variable: encounters = total # of health care encounters
(Total # of health care encounters = # of office-based visits + # of emergency department visits + # of hospital admissions)

i. <u>Office-based visits</u>:
- From OHIP data, use %ohip_location macro to define the location of OHIP claims for 'Consultations and Visits' (Section A of the OHIP Fee Schedule)
- Identify claims where the location is in (a) office; (b) home; (c) phone; (d) long-term care; (e) undefined [*location = office, home, phone, ltc, undefined; keep = ikn, physnum, servdate, feecode; keepextra = location*]
- Aggregate all claims by the same physician provided to the same patient on the same day (i.e. count as <u>one</u> health care encounter) and count the number of unique encounters for all office-based visits

ii. <u>Emergency room visits</u>:
- From OHIP data, use %ohip_location macro to define the location of OHIP claims
- Identify claims where the location is an ER [*location = ER; keep = ikn, physnum, servdate, feecode; keepextra = location*]
- 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

iii. <u>Hospital admissions</u>:
- From CIHI-DAD data, use *epi* (i.e. episodes of care – series of linked hospital admissions)
- Count the number of unique hospital admissions (i.e. unique *epi* number)

2. **Continuity of care – Usual Provider Continuity (UPC) Index – in 3 to 27 months before index event**
   Variable: upc = value between 0 and 1 or undefined
   (UPC = n_i / N; only defined for individuals with 3 or more visits (i.e. N ≥ 3) in defined period of time)
   i. N = total number of visits to a GP/FP (in office, phone, home, long-term care facility, or undefined; see 'Number of health care encounters' variable)
      - 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)
      - Get total number of visits for all individuals
   ii. n_i = number of visits to the usual provider (the usual provider is the physician who provides the greatest proportion of care)
      - Visits to a specialist are attributed to the GP/FP who referred the patient (included in UPC calculation)

Note: Look back windows for the use of preventive services variables (#3-7) include a 12-month buffer added to the recommended intervals of use.

3. **Physical examination in 3 to 27 months before index event**
   Variables: (1) physical_exam = Yes/No; (2) exam_count = # of physical exams
   - From OHIP data, individual had a physical exam if:
     i. *feecode = A003 and dxcode = 917*

4. **Influenza vaccination in 3 to 27 months before index event**
   Variables: (1) flu_shot = Yes/No; (2) flu_count = # of flu vaccinations
   - From OHIP data, individual was vaccinated if either:
     i. *feecode = G590 or G591* (in any month)
     ii. *feecode = G538 or G539* (in October and November only)

5. **Breast cancer screening (mammography) in 3 to 39 months before index event** *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 – duration of eligibility
   - Woman was screened, if either:
     i. From OBSP SCREEN data, *screened = 2 or 3*
     ii. From OHIP data, *feecode = X185*

6. **Cervical cancer screening (Pap test) in 3 to 51 months before index event**
   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 duration of eligibility
   - From OHIP data, woman was screened if there is at least one of:
     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 look back window)

i. From OHIP data, *feecode = S810, S757, S758, S816, S710, S763, S762, S727, S765, S766, or S767*

7. **Colorectal cancer screening in look back window before index event:**
   - For males and females who were aged 50 to 74 years at any time during the specified look back windows of each test – include duration of eligibility
   - From OHIP data, individual was screened if there is at least one:
     i. **Fecal Occult Blood Test in 3 to 39 months before index event**
     Variables: (1) fobt = Yes/No/Missing; (2) fobt_count = # of fecal occult blood tests; (3) fobt_eligible = duration of eligibility
     - Fecal occult blood test: *feecode = L181 or G004*

     ii. **Sigmoidoscopy or barium enema in 3 to 75 months 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 = Z580 or Z555 (without E740, E741, E747, or E705 on the same day)*
     - Single contrast barium enema: *feecode = X112*
     - Double contrast barium enema: *feecode = X113*

     iii. **Colonoscopy in 3 to 135 months before the index event**
     Variables: (1) colonoscpy = Yes/No/Missing; (2) colon_count = # of colonoscopies; (3) colon_eligible = duration of eligibility
     - Colonoscopy: *feecode = Z555 plus one of E740, E741, E747, or E705 on the same day*

8. **Enrolment in primary care program in 3 to 27 months before index event**
   Variable: primarycare = Yes/No
   - From CAPE data, get *startcape* and *endcape*:
     i. *primarycare = 1* if *startcape* = 'before date at the start of look back window (i.e. 27 months prior to index)' and *endcape* = 'missing'
     ii. *primarycare = 0* if *endcape* = 'before date at the start of look back window' or there is no record in CAPE

Baseline Characteristics

1. **Age at index event**
   Variable: age = age in years
   - Use %getdemo macro to get *age*; where *agedate* = 'date of diagnosis for laryngeal cancer cohort' or 'index date for comparison cohort'
2. **Sex**
   Variable: sex = Male/Female
   - Use %getdemo macro to get *sex* (i.e. *getsex* = T)
3. **Urban/rural residence at 27 months before the index event**
   Variable: urban = Large urban/Small urban/Rural/Missing
   - Use %getdemo macro to get *rio2008* and *prcddablk* (i.e. *geovars = rio2008, prcddablk*); where *geodate* = 'date at 27 months before the index event'
     i. *urban = 1* if $0 \leq rio2008 \leq 9$ and non-missing
     ii. *urban = 2* if $10 \leq rio2008 < 40$ and non-missing
     iii. *urban = 0* if $rio2008 \geq 40$ or *rio2008* = missing but *CSD01* is valid (*prcddablk)*
     iv. *urban = missing* otherwise (i.e. if *rio2008* and *CSD01* are missing or invalid)

	4. Socioeconomic status – Neighbourhood Income Quintiles – at 27 months before the index event *Variable: incquint = 1/2/3/4/5* - Use %getdemo macro to get *prcdda* and *incquint* (i.e. *geovars=prcdda, incquint*); where *geodate*='date at 27 months before the index event' **5. Co-morbidities – Aggregated Diagnosis Groups (ADGs) – within 3 to 27 months before the index event:** *Variables: sum_madg = value between 0 and 8; sum_adg = value between 0 and 32* - Use %getacg macro to get *acgvars = ADG1-ADG34* using diagnoses from OHIP and CIHI-DAD data within 3- to 27-month look back window i. Total number of major ADGs (3, 4, 9, 11, 16, 22, 25, 32) ii. Total number of ADGs (maximum = 32)
Other Variables	**1. RCC Number:** From OCR data, get *rcc* **2. RCC Registration Date:** From OCR data, get *rcc_regdate* **3. LHIN of residence at 27 months before the index event** - Use %getdemo macro to get *lhin* (i.e. *geovars = lhin*); where *geodate* = 'date at 27 months before index event' **4. County of residence at 27 months before the index event** - Use %getdemo to get *cnty* (i.e. *geovars = cnty*); where *geodate* = 'date at 27 months before the index date'
Outcome Definitions	**TNM stage at diagnosis** *Variables: (1) stage = TNM stage group I-IV (2) stage_gp = stage I/II or stage III/IV* - From CCE Stage File i. Clinical stage: stage group and individual T, N, and M categories (i.e. *clinical_stage_at_diag, clinical_stage_T_at_diag, clinical_stage_N_at_diag, clinical_stage_M_at_diag*) ii. Pathological stage: stage group and individual T, N, and M categories (i.e. *path_stage_at_diag, path_stage_T_at_diag, path_stage_N_at_diag, path_stage_M_at_diag*) iii. Derive stage group from T, N, and M categories (clinical and pathological): 1. If M='M1' or N='N3' or T=T4, then *stage = 'IV'* 2. If T or N are missing or unknown, then *stage = 'missing'* (If M is missing assume M='M0'.) 3. If N='N3' or T='T3', then *stage = 'III'* 4. If T='T2' then *stage = 'II'* 5. If T='T1' then *stage = 'I'* iv. Combine variables: *stage = 'I/II or III/IV'*

Outline of Analysis Plan

Descriptive analyses to examine the distribution of demographic characteristics (i.e. age, sex, socioeconomic status, rural residence, and urban/rural residence) in the laryngeal cancer cohort and the comparison cohort. For the laryngeal cancer cohort, cancer subsite and stage at diagnosis will also be described.

Objective 1: Bivariate analyses of usual health care utilization among laryngeal cancer patients will be conducted for all laryngeal cancers. Frequency of health care encounters, type of health care encounters (i.e. physical examination, cancer screening, influenza immunization, enrolment in primary care program), and the degree of continuity of care will be compared across all stage groups (I-IV) and between patients with early (Stages I and II) and advanced (Stages III and IV) disease. Continuous variables will be compared using two sample t-tests or Wilcoxon rank sum tests and categorical variables will be compared using chi-square tests.

Binomial regression will be used to investigate the strength of association between usual health care utilization variables and stage at diagnosis. The independent effect of each of these variables on disease stage will be examined, while simultaneously controlling for other variables (i.e. baseline characteristics). Subsite will be considered as a potential effect modifier in the multivariate analyses. Backwards elimination will be used to select and adjust for covariates.

Sensitivity analyses will be performed to assess misclassification of stage at diagnosis. The distribution of time between the date of diagnosis and registration at a RCC will be examined. Patients seen at a RCC after 30, 60, and 90 days from diagnosis will be excluded in the sensitivity analyses.

Objective 2: Similar bivariate analyses will be conducted to describe and compare usual health care utilization between the laryngeal cancer cohort and the comparison cohort. Conditional logistic regression will be used to adjust for baseline characteristics and determine if laryngeal cancer patients use health care differently than the general population.

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

Queen's University

December 20, 2010

This Ethics Application was subject to:

☐ Full Board Review
Meeting Date:
☒ Expedited Review

Ms. Felicia Leung
Department of Community Health and Epidemiology
Division of Cancer Care and Epidemiology
Queen's Cancer Research Institute, Level 2
Queen's University

Dear Ms. Leung,

Study Title: **The association between usual health care utilization and stage at diagnosis in laryngeal cancer**
Co-Investigators: **Dr. Patti Groome and Dr. Stephen Hall**

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol 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 list 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. (see http://www.queensu.ca/vpr/reb.htm).
- **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.
- **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 Clark
Chair, Research Ethics Board

Jan 3, 2011
Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD- COPY TO HOSPITAL - BINDER COPY - FILE COPY

Study Code: EPID-333-10

- **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 C MINIMUM DETECTABLE DIFFERENCES

Table C-1. *A priori* minimum detectable differences between early- and advanced-stage laryngeal cancer, to achieve 80% power and two-sided significance level of 0.05.

Frequency of Health Care Encounters
Based on the distribution of health care encounters 24-months prior to diagnosis observed in oral cavity cancer, we expect a mean of 15 encounters and standard deviation of 17.4 encounters.

Subsite	Detectable Difference	Power
Larynx (*n* = 1,243)	2.9 encounters	80%
Glottic (*n* = 825)	4.4 encounters	80%
Supraglottic (*n* = 418)	5.0 encounters	80%

Annual Physical Examination
Based on health care utilization data for oral cavity cancers, we expect 9% of the population to have a physical exam before diagnosis.

Subsite	Detectable Difference	Power
Larynx (*n* = 1,243)	4.9%	81%
Glottic (*n* = 825)	7.6%	80%
Supraglottic (*n* = 418)	8.1%	80%

Enrolment in a Primary Care Model
Based on 20.9% of family or general physicians in Ontario reporting that their main patient care setting is an inter-professional practice.

Subsite	Detectable Difference	Power
Larynx (*n* = 1,243)	6.9%	81%
Glottic (*n* = 825)	10.6%	80%
Supraglottic (*n* = 418)	11.6%	80%

Continuity of Care
Based on health care utilization data for oral cavity cancers, we expect 55.5% of the population to have high continuity of care (UPC ≥ 0.6).

Subsite	Detectable Difference	Power
Larynx (*n* = 1,243)	8.3%	80%
Glottic (*n* = 825)	12.6%	80%
Supraglottic (*n* = 418)	14.4%	80%