Understanding the extent of polypharmacy and its impact on outcomes among persons with

cancer and multimorbidity

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including

any required final revisions, as accepted by my examiners. I understand that my thesis may be

made electronically available to the public.

Abstract

Background: Cancer often co-occurs with other chronic conditions, and despite the high prevalence of multimorbidity (MMB) in this group, conditions are often treated individually, resulting in multiple prescriptions. Polypharmacy commonly defined as the use of five or more medications, is more common among people with MMB and is associated with a number of adverse outcomes (i.e., increased health service utilization and death). The literature sufficiently describes the occurrence and associated adverse outcomes among older adults; however, there are limited studies on this topic in younger adults.

Objectives: The aim of this current study is to examine polypharmacy and its impact among adults 18 years or older with cancer and other chronic diseases. Specifically, it examines the prevalence of polypharmacy across age, sex, MMB level, and type of cancer. It also assesses the relationship between polypharmacy, high use of health services (i.e., emergency room visits, hospitalization) and death, while controlling for other factors.

Methods: This study utilized a quantitative, retrospective longitudinal design, based on linked provincial health administrative data available from the Institute for Clinical Evaluative Services. The study population consisted of persons diagnosed with cancer between April 1, 2012 to March 31, 2013. They were followed to identify high use of emergency room visits and hospitalizations within one year (i.e., until March 2014); the 90th percentile margin was used to define "high user" and death was measured until March 31, 2018. Bivariate analysis using Chi-squared statistic was completed to assess the association between differences in. polypharmacy across age groups, sex, MMB level, and type of cancer. The interaction between MMB level, sex, age, and polypharmacy after a cancer diagnosis was also evaluated. Multivariate logistic

regression models were developed to examine the relationship between polypharmacy and high use of emergency room visits, high use of hospitalizations, and death.

Results: The majority of the study population was females, aged 65+ years, and had at least one condition besides cancer. The overall prevalence of polypharmacy was 46.5% prior to cancer diagnosis and 57.1% within one year after. Polypharmacy increased with level of MMB (from 13.8% among those with no chronic condition, to 55% among those with 3+ conditions). The highest prevalence of polypharmacy was observed in persons aged 65+ years (55.3%), those with lung and bronchus cancer (53.5%), and stage 4 cancer (53.8%); there was no meaningful difference by sex. The prevalence of polypharmacy was lowest in 18-44 year old females with no chronic conditions (7.5%) and highest in 65+ year females with 3+ conditions (64.9%). Overall, 10.7% of persons were considered "high users" of emergency room services, 21.3% of hospitalizations, and 26% died between one year post-cancer diagnosis and the end of follow-up in 2018. In the multivariate models, hyper-polypharmacy was significantly associated with a 34% increase in the odds of being a high user of emergency room services, and 19% for high use of hospitalizations. Polypharmacy and hyper polypharmacy (10+ medications) were also associated with a 1.3 and twofold increase in risk of death. In each of the multivariate models, male sex and increasing levels of MMB were associated with increased likelihood of being a high user of both services and death. In particular, compared to having a diagnosis of cancer only, the presence of 3+ other chronic conditions was associated with an 82%, 41%, and 36% increase in those odds, respectively. Older age was associated with a decreased risk of being a "high user" of health services and an increased risk for death.

Conclusion: The results of this study provide evidence about the impact of polypharmacy among adults 18 years and older with cancer and multimorbidity.

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Chapter 1: Introduction

Cancer is the second leading cause of mortality worldwide (Global Burden of Disease, 2016; Nagai & Kim, 2017) and the burden of cancer is increasing globally, as a result of varied at-risk behaviours and the growth of an aging population (Jemal et al., 2011). According to the Canadian Cancer Statistics (2019) one in two Canadians will be diagnosed with cancer in their lifetime, with an estimated 220,400 new cases in 2019. The risk of cancer increases with age, where 90% of newly diagnosed cases will consists of Canadians over the age of 50 years (Canadian Cancer Statistics, 2019); it is also higher among males.

The prevalence of multimorbidity, defined as the co-occurrence of two or more chronic health conditions, is increasing among older persons (Afshar, Roderick, Kowal, Dimitrov, & Hill, 2015), and many elderly persons are living longer with multiple chronic diseases (Sarfati, Koczwara, & Jackson, 2016). The Canadian Institute for Health Information (2011) states that Canadians 65 years and older experience a disproportionate health burden due to multimorbidity; older adults were four times more likely to be diagnosed with a chronic condition than adults between the ages of 18 and 24. Cancer is also considered a chronic disease that is prevalent in the elderly, and therefore multimorbidity among persons with cancer is common (Safarti et al., 2016). There is a wide reported prevalence range of 0.4% to 90% of multimorbidity among persons with cancer (Lee, Cheung, Atkinson, & Krzyzanowska, 2011; Sarfati, Hill, Purdie, Dennett, & Blakely, 2010; van Doorn et al., 2001). Multimorbidity can affect the stage of cancer at diagnosis, the pathophysiology of cancer, and the pharmacological management of cancer (Gurney, Sarfati, & Stanley, 2015; Safarti et al., 2016). While the symptoms of chronic diseases may prompt an individual to seek medical help and therefore, they are diagnosed sooner with cancer, the reverse may also occur (i.e., symptoms of cancer may be misinterpreted as another

chronic disease and the diagnosis of cancer may be delayed; Gurney et al., 2015). Another challenge related to multimorbidity is polypharmacy, as each co-occurring condition may require different therapeutic approaches.

Polypharmacy has various definitions, it is defined by numerical groupings with associated terms such as hyper polypharmacy or excessive polypharmacy (Bushardt, Massey, Simpson, Ariail, & Simpson, 2008; Gnjidic et al., 2012; Masnoon et al., 2017; Nightingale et al., 2014; Sirois et al., 2019), or by a descriptive definition such as appropriate or inappropriate polypharmacy (Bushardt, Massey, Simpson, Ariail, & Simpson, 2008; Maggiore, Gross, & Hurria, 2010; Masnoon et al., 2017). In the literature the most common definition is the use of five or more drugs (Gnjidic et al., 2012; Masnoon et al., 2017; Prithviraj et al., 2012).

Polypharmacy can also be used to describe potentially inappropriate medications, excessive drugs, drugs with no therapeutic indication or unnecessary drugs (LeBlanc, McNeil, Kamal, Currow, & Abernethy, 2015; Maggiore, Gross, & Hurria, 2010; Mortazavi et al., 2016), and it is linked to drug therapy related problems (Golchin, Isham, Meropol, Vince, & Frank, 2015). For example, polypharmacy that results in potentially inappropriate medication can increase the risk for adverse drug events and drug therapy duplications (Hajjar, Cafiero, & Hanlon, 2007; Hanlon, Schmader, Ruby, & Weinberger, 2001). The quantity of medications prescribed is not suggestive of whether a drug is appropriate, as all drugs prescribed may have a therapeutic benefit in some individuals regardless of the number (Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017; Rambhade, Chakarborty, Shrivastava, Patil, & Rambhade, 2012). Inappropriate medications or potentially inappropriate medications are defined as drugs with a risk for a harmful effect that outweighs the therapeutic benefit of the drug, and there is clinical evidence to support an alternative drug that is safer and more effective; also, it may be the case

when an incorrect dose and duration of therapy is prescribed (Beuscart, Dupont, Defebvre, & Puisieux, 2014; Corsonello et al., 2012; Mimica Matanović, & Vlahovic-Palcevski, 2012). Therefore, the appropriate quantity of medications that should be prescribed is variable, and is specific to the individual's physiological status, life expectancy and the preference of the clinicians (Steinman, & Hanlon, 2010).

Polypharmacy may be a consequence of both cancer (Nightingale, Hajjar, Swartz, Andrel-Sendecki, & Chapman, 2015) and multimorbidity (Calderón-Larrañagaet al., 2012). For example, a more advance cancer disease is linked to an even higher number of medications (Currow, Stevenson, Abernethy, Plummer, & Shelby-James, 2007). Cancer site may also be a factor. In a case control study that included 480,000 elderly persons with all incident cancer cases in Denmark, lung cancer had the strongest association to polypharmacy compared to the other cancer types (Jorgensen, Herrstedt, Friis, & Hallas, 2012). Not surprisingly, persons with cancer and multimorbidity have an increased number of medications prescribed (Masnoon et al., 2017). The pharmacological management of persons with cancer and multimorbidity is complex, as medications are prescribed to treat the malignancy, the concomitant illnesses and any drug therapy related toxicity that may occur (Prithviraj et al., 2012). The type and severity of chronic disease in persons with cancer is also positively associated with the number of medications prescribed (Lichtman, & Boparai, 2008; Turner, McKinnon, & Bell, 2016).

Other factors associated with polypharmacy include age and sex. Increased age is a risk factor for polypharmacy (Balducci, Goetz-Parten, & Steinman, 2013; Hosseini, Zabihi, Jafarian Amiri, & Bijani, 2018); older adults are the principal consumers of medications (Sergi, De Rui, Sarti, & Manzato, 2011). In Canada approximately one-quarter of elderly people are prescribed 10 or more medications (Canadian Institute for Health Information, 2016). The occurrence of

potentially inappropriate medications is also common among older adults (Gallagher, Barry, & O'Mahony, 2007). The number of medications prescribed increases the risk for adverse drug events and harm (Marcum et al., 2012; Proulx, 2018; Reason et al., 2012). Being female is also a risk factor for polypharmacy, as is the combination of being female and age 85 years and older, (Jensen, & Schroll, 2008; Jyrkkä, Enlund, Korhonen, Sulkava, & Hartikainen, 2009a). As a result of the increased risk of polypharmacy in older females compared to males, they are more susceptible to potential adverse effects related to polypharmacy caused by inappropriate medications (Bierman et al., 2007; Morgan et al., 2016; Santos et al., 2015).

Pharmacotherapy plays an integral role in cancer treatment. Chemotherapeutic agents are very toxic, resulting in many drug related problems that require immediate attention (Vantard et al., 2015). The added adverse events incurred by polypharmacy can increase the incidence of health service utilization, such as emergency room visits and hospitalizations, especially in the elderly (Ahmed, Nanji, Mujeeb, & Patel, 2014; Beer et al., 2011; Calderón-Larrañaga et al., 2012; Reason et al., 2012; Scott et al., 2015) or even death.

The prevalence of polypharmacy and the associated negative health outcomes among older adults with cancer and multimorbidity has been extensively discussed in the literature, however the prevalence and impact of polypharmacy among younger adults with cancer and other chronic diseases is not adequately represented in the literature.

The aim of this study is to better assess the issue of polypharmacy and its impact among both young and old adults 18 years or older with cancer and other chronic diseases. Specifically, it will determine whether the prevalence of polypharmacy differs by age, sex, multimorbidity and type of cancer. The study will also assess the relationship between polypharmacy, and health

service utilization (i.e., emergency room visits and hospitalization) and death in this group, while controlling for other factors.

Chapter 2: Literature Review

Cancer

Cancer is the abnormal growth of cells, that can originate from any structure in the body or organ (Roy & Saikia, 2016). It is a primary cause of death worldwide; in 2018, a global estimate of 18.1 million persons were newly diagnosed with cancer and 9.6 million persons succumbed to this diagnosis (Ferlay et al., 2019). The incidence of cancer cases is expected to increase, and deaths from cancer will also increase as the population grows, which contributes to the burden of cancer (Torre, Siegel, Ward, & Jemal, 2016).

Age is the most significant risk factor for cancer (Canadian Cancer Society, 2019); the rates of cancer are at the highest in females between the ages of 80 to 84 years and at the age of 85 years in males. For both males and females, cancer is most likely diagnosed between the ages of 65 to 69 years. The incidence of cancer is higher in females than in males between the ages of 25 years and 59 years, however, the incidence rates are higher in males for all other age groups (Canadian Cancer Society, 2019).

Certain types of cancers vary by age groups (Canadian Cancer Society, 2019), where 99% of lung cancers and 98% of prostate cancers are diagnosed in persons 50 years and older. Approximately 40% of all breast cancers are diagnosed in females between the ages of 30 to 59 years, and 56% of colorectal cancers occur in persons between the ages of 50 to 74 years (Canadian Cancer Society, 2019). Ferlay et al., (2019), reported that lung cancer and breast cancer are more prevalent in males and females, respectively. Brenner et al. (2020) projects that in the year 2020 the incidence of cancer in Canada will increase to 225,800 people, with the

prevalence being higher in Canadian males. Lung cancer will be the most diagnosed, followed by breast cancer, colorectal cancer and prostate cancer in that order; prostate cancer will be the most diagnosed cancer in Canadian males and breast cancer will be more commonly diagnosed in Canadian females (Brenner et al., 2020).

A diagnosis of cancer is associated with various risk factors, which include lifestyle behaviours such as smoking, reproductive patterns, excess body weight, unhealthy diet, a sedentary lifestyle, and alcohol consumption (Torre et al., 2016), or factors that can not be controlled, such as inherited cancer predisposition or age (National Cancer Institute, 2015).

The worldwide estimated mortality for cancer in 2018 was 9.6 million (Bray et al., 2018), it is projected that an estimated 83,300 Canadians will die from cancer in 2020 (Brenner et al., 2020). According to Brenner et al. (2020) lung cancer will be the number one cause of cancer related mortality in males and females, contributing to more deaths in Canada in 2020 than the 3 leading causes; breast, colorectal and pancreatic cancer combined. In Canada, prostate, lung, breast, pancreatic, and colorectal cancers will account for 55% of the predicted cancer deaths, males will have a higher incidence of mortality than Canadian females (Brenner et al., 2020). Cancer often co-occur with one or more additional chronic diseases.

Multimorbidity

Multimorbidity has also been described as a global public health dilemma, and a burden on the health care system (Pathirana & Jackson, 2018). Multimorbidity is defined as the co-occurrence of two or more chronic diseases (Feely, Lix, & Reimer, 2017; Koné Pefoyo et al., 2015; Makovski, Schmitz, Zeegers, Stranges, & van den Akker, 2019; Marengoni et al., 2011; Rosbach & Andersen, 2017; Yarnall et at., 2017), and is commonly measured using a predefined list of chronic conditions (Koné Pefoyo et al., 2015; Roberts, Rao, Bennett, Loukine, &

Jayaraman, 2015). In Canada, 74% of persons have been diagnosed with one or more chronic diseases (Canadian Institute for Health Information, 2011; Roberts, Rao, Bennett, Loukine, & Jayaraman, 2015; Sakib, Shooshtari, St John, & Menec, 2019).

The prevalence of multimorbidity has increased worldwide, which has been attributed to longer life expectancies due to advances in medical care and the implementation of public health policies (Barnett et al., 2012; Boyd & Fortin, 2010; Fortin et al., 2006; Islam et al., 2014; Koné Pefoyo et al., 2015; Pathirana & Jackson, 2018). The incidence of multimorbidity has surpassed infectious diseases (Marengoni et al., 2011). Estimates of the prevalence of multimorbidity varies from 13.1% to 90% (Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Menotti et al., 2001).

A systematic review that included 41 articles carried out by Marengoni et al. (2011), aimed to summarize existing scientific literature available regarding the occurrence, causes, and consequences of multimorbidity among older adults. Cross sectional studies including people 60 years and older showed that the prevalence of multimorbidity ranged from 55% to 98%, where older age, female sex, and low socioeconomic status were all factors associated with multimorbidity (Agur, McLean, Hunt, Guthrie, & Mercer, 2016; Marengoni et al., 2011); sedentary lifestyle, excessive alcohol intake, unhealthy diet, smoking and being overweight have also been identified as risk factors (Fortin et al., 2014). These risk factors are also common to many cancers (Koene, Prizment, Blaes, & Konety, 2016; Ogle, Swanson, Woods, & Azzouz, 2000).

Cancer and Multimorbidity

Multimorbidity is more prevalent among older adults with cancer compared to persons in an age-matched control group without cancer (Jørgensen et al., 2012; Williams et al., 2016).

Increased age is a shared risk factor for both cancer and multimorbidity, therefore, it is common that elderly people with cancer have several other chronic diseases (Jørgensen et al., 2012; Sarfati et al., 2016; Smith et al., 2008; Wedding et al., 2006). The prevalence of multimorbidity and cancer differ by age, (Cancer Care Ontario, 2018; Elena et al., 2013; Fowler et al., 2020; Li, Fitzgerald, & Rodin, 2012; Sørensen, 2013). The results of a retrospective cohort study that included 331,655 people between the ages of 15 years and 90 years who were diagnosed with one of four different types of cancer, colon, rectum, lung, or Hodgkin's lymphoma showed that younger people with cancer had less concurrent chronic diseases compared to older people with cancer (Fowler et al., 2020). Approximately 29.2% of people diagnosed with lung cancer between the ages of 15-29 years old had one concurrent chronic disease and 3.4% had more than one other chronic disease, persons between the ages of 75 to 90 years with multiple chronic diseases and one other chronic disease was 49.9% and 26.9% respectively (Fowler et al., 2020).

The prevalence of multimorbidity also differs by type of cancer (Cancer Care Ontario, 2018; Edward et al., 2014; Fowler et al., 2020). For example, lung cancer and bladder cancers are more commonly associated with other chronic diseases, whereas persons with breast cancer and melanoma have a lower prevalence of multimorbidity (Jørgensen et al., 2012; Safarti et al., 2016). Fowler et al. (2020), examined the prevalence of 14 predefined chronic diseases by type of cancer. The results of the study showed that persons diagnosed with lung cancer had the highest prevalence of multimorbidity (67%) and the prevalence of multimorbidity in persons with Hodgkin lymphoma was 30% lower than persons with lung cancer (Fowler et al., 2020). Data retrieved from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database that included a total of 1,056,534 people with cancer and 100,000 persons without cancer (Edwards et al.,2014), showed the prevalence of a selected

number of chronic diseases in persons aged 66 years and older with cancer was similar in persons with breast cancer (31.8%), prostate cancer (30.5%) and persons who were cancer-free (31.8%) (Edwards et al.,2014). Persons with lung cancer and colorectal cancer had the highest prevalence of chronic diseases, 59% and 40.7% respectively. Reports from the Ontario Cancer Statistics (2018) show similar findings, persons with lung cancer had the highest prevalence of multimorbidity and those with breast cancer had the lowest prevalence.

The data reported by Edwards et al. (2014) shows the most prevalent diseases in people with cancer were diabetes mellitus, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD). In Ontario, of the five most common chronic diseases by cancer type, diabetes mellitus was most prevalent in persons diagnosed with bladder cancer, breast cancer, colorectal cancer, and pancreatic cancer (Ontario Cancer Statistics, 2018). There are also other studies that demonstrated an inverse correlation between certain types of cancer and Alzheimer disease (Benito-León, Romero, Louis, & Bermejo-Pareja, 2014; Li et al., 2014; Majd, Power, & Majd, 2019; Roe et al., 2010; Seo & Park, 2020). In a population-based study that included people aged 60 years and older, Musicco et al. (2013), assessed the incidence of cancer in persons with Alzheimer disease and the incidence of Alzheimer disease dementia in persons with cancer. They reported that the occurrence of various types of cancers in patients with Alzheimer disease and of Alzheimer disease in persons with cancer were both decreased, this lower incidence became statistically significant in adults 70 years and older (Musicco et al., 2013).

The treatment of persons with cancer and multimorbidity is generally less likely to be curative, compared to the management of persons with cancer and no multimorbidity (Koppie et al., 2008; Lee et al., 2011; Rodrigues & Sanatani, 2012; Safarti et al., 2016). Multimorbidity can

impact the selection of cancer therapy and how well persons tolerate drug therapy (Safarti et al., 2016). For example, people with cancer with concurrent renal disease may not be prescribed a certain class of chemotherapy due to possible nephrotoxicity, but may be prescribed other drugs (Grønberg et al., 2010; Gross, McAvay, Guo, & Tinetti, 2007; Vickers et al., 2012). Drug therapy is the most common treatment modality for chronic diseases including cancer, persons with cancer and multimorbidity are exposed to polypharmacy (Barnett et al., 2012; Lees & Chan, 2011; Turner, Kantilal, Kantilal, Holmes, & Koczwara, 2020).

Polypharmacy

Polypharmacy is variously defined as the use of five or more medications in one individual (Gnjidic et al., 2012; Masnoon et al., 2017; Turner et al., 2016; Wongpakaran et al., 2018), and is the most commonly used definition (Masnoon et al., 2017). Similarly, to multimorbidity, it is common among older adults (Masnoon et al., 2017). However, it should be noted that polypharmacy is not always harmful and the clinical reasons for prescribing multiple medications should be a considered (Payne, 2016; Prithviraj et al., 2012; Tuner et al., 2016). Risk factors for polypharmacy include increased age, sex, multimorbidity, multiple physicians at one point in time, and prescriptions dispensed at multiple pharmacies (Calderón-Larrañagaet al., 2012; Lees & Chan 2011; Lichtman & Boparai, 2008; Maggiore et al., 2010; Morio et al., 2019; Payne, 2016).

In Canada it is estimated that 69% or 1.8 million people 65 years and older are prescribed 5 or more medications over one year, with the prevalence reported to be higher in adults 85 years and older (McPherson, Ji, Hunt, Ranger, & Gula, 2012). The health insurance claims from six provinces in Canada, showed that 62% of elderly persons enrolled in public drug programs, were dispensed 5 or more drug classes at one time, this is because of the aging Canadian population

and increased prevalence of multimorbidity (Reason et al., 2012). In a survey funded by the

Canadian Institute for Health Information and the Health Council of Canada conducted between

April and June of 2008, there were a total of 11,582 respondents 18 years and older, which

included 3,132 older adults; it had an overall response rate of 71% (Reason et al., 2012). The

investigators set out to determine the impact of polypharmacy and adverse drug events among

older Canadians (i.e., 65-74 years, 75-84 years and 85 years and older), and asked if they were

diagnosed with multiple chronic diseases and how many prescribed medications they were taking

at the time (Reason et al., 2012). The survey results showed 27% of elderly respondents under

the age of 85 years reported that they took 5 or more medications regularly, and 41% of persons

85 years and older reported taking 5 or more medications regularly.

The literature reports differences in the prevalence of polypharmacy between men and

women, with the reported prevalence higher in women (Feng et al., 2018; Moen et al., 2009;

Morgan et al., 2016; Rozenfeld, Fonseca, & Acurcio, 2008). For example, after adjusting for age

and multimorbidity males were prescribed less drugs than females (Skoog, Midlöv, Borgquist,

Sundquist, & Halling, 2014). There are few contradicting studies that report a higher prevalence

of polypharmacy in men (Chan, Hao, & Wu, 2009; Jyrkkä et al., 2009a; Slabaugh, Maio,

Templin, & Abouzaid, 2010). These differences in the prevalence of polypharmacy (PIM)

between men and women were reported to be related to differences in physician prescribing

practices, differences in socioeconomic status and educational characteristics between men and

women (Bierman et al., 2007; Slabaugh et al., 2010).

The diagnosis and therapeutic management of men compared to women differ which

influences the type and number of drugs prescribed (Hajjaj et al., 2010; Krieger,2003; Moen et

al., 2009). Gender-related morbidity also influences the prevalence of polypharmacy (Skoog, et

al., 2014), as there are considerable gender differences in drug therapy management and health service utilization between women and men, with women seeking preventive medical care more often than men, thus resulting in more prescribed drugs (Galdas, Cheater, & Marshall, 2005; Holmes, Luo, Kuo, Baillargeon, & Goodwin, 2013; Redondo-Sendino, Guallar-Castillón, Schappert, & Burt, 2006; Skoog et al., 2014; Tannenbaum et al., 2017; Thompson et al., 2016).

Polypharmacy is a predisposing factor for drug-drug interactions in older adults. The results of a prospective cohort study that included elderly persons with polypharmacy reported a prevalence of potential drug-drug interaction to be 80% (Maher, Hanlon, & Hajjar, 2014). Adverse drug events are harmful unintended reactions to medications, they are common reasons for medical care that result in elevated morbidity and medical expenses (Bourgeois, Shannon, Valim, & Mandl, 2010; Coleman & Pontefract, 2016). The probability of a drug-drug interaction increases in persons taking 5 to 9 medications is about 50% (Doan, Zakrzewski-Jakubiak, Roy, Turgeon, & Tannenbaum, 2013). The risk of drug-disease interactions also increases as a result of polypharmacy (Lindblad et al., 2006), chemotherapeutic agents and supportive drug therapies can increase this risk in people with cancer (Lee & Chan, 2011).

Polypharmacy and Cancer

The number of medications prescribed for persons diagnosed with cancer varies by: cancer related toxicities and drug therapy related problems (Turner et al., 2014), multimorbidity (Prithviraj et al., 2012), stage of cancer (Kierner, Weixler, Masel, Gartner, & Watzke, 2015; Puts et al., 2009; Turner et al., 2014), and type of chemotherapy management (Maggiore et al., 2010; Sokol, Knudsen, & Li, 2007). There is sparse literature on polypharmacy specifically in older adults with cancer (Flood, Carroll, Le, & Brown, 2009; Sokol et al., 2007) and even less on

younger adults, though some have reported prevalence between 11% and 96% (Lees & Chan, 2011; Maggiore et al., 2010; Nightingale, et al., 2015; Prithviraj et al., 2012; Turner et al., 2016).

Unnecessary medications increase the risk of adverse drug events (Bushardt, Massey, Simpson, Ariail, & Simpson, 2008) and polypharmacy in elderly persons with cancer (Maggiore et al., 2010). Unnecessary medications include drugs with no documented clinical indication, clinically ineffective drugs, and therapeutic duplications (Golchin et al., 2015; Jyrkkä et al., 2009a; Rossi et al., 2007). Unnecessary polypharmacy is positively associated with unplanned hospitalizations caused by adverse drug events (Budnitz, Shehab, Kegler, & Richards, 2007; Marcum et al., 2012), and when unnecessary medications are concurrently administered with chemotherapeutic agents, they increase the risk of drug therapy related toxicity and high use of health services (Dedhiya, Hancock, Craig, Doebbeling, & Thomas 2010; Elliot et al., 2014; Espino et al., 2006; Iwata, Kuzuya, Kitagawa, Suzuki, & Iguchi, 2006; Kotlinska-Lemieszek Paulsen, Kaasa, & Klepstad, 2014).

Polypharmacy and Multimorbidity

As stated in the previous section, the prevalence of polypharmacy increases with age (Fano, Chini, Pezzotti, & Bontempi, 2014), and there is a higher incidence of multimorbidity among older adults, which requires multiple drug therapy management (Feng et al., 2018; Mannucci, Nobili, & REPOSI Investigators 2014; Vrettos, Voukelatou, Katsoras, Theotoka, & Kalliakmanis, 2017). Physicians prescribing all required drugs based on clinical disease-oriented guidelines can result in polypharmacy. For example, the cardiovascular disease drug regimen is complex and require multiple drugs (Al Ameri, Makramalla, Albur, Kumar, & Rao, 2014; Appleton, Abel, & Payne, 2014; Bierman et al., 2007; Boyd et al., 2005; Feng et al., 2018; Mannucci & Nobili, 2014; Scott, Blizzard, Fell, & Jones, 2009; Vrettos et al., 2017; Wong,

Chaudhry, Desai, & Krumholz, 2011). Certain chronic diseases have a stronger relationship to polypharmacy compared to others (Al Ameri et al., 2014; Bierman et al., 2007; Nightingale et al., 2015; Vrettos et al., 2017). In a cross-sectional study that included 38,329 Medicaid enrollees between the ages of 45 to 64 years with multimorbidity (Feng et al., 2018), the authors aimed to determine the association between polypharmacy and multimorbidity (from a predefined list of conditions), and inappropriate medications. Feng et al. (2018) reported that 64.9% of persons were exposed to polypharmacy, the majority were women, and the two most prevalent coexisting chronic diseases were hypertension and hyperlipidemia; polypharmacy was shown to be positively associated with multimorbidity and varied among different chronic diseases.

The requirement of multiple drugs to manage diseases or harmful unintended drug effects can potentially result in the diagnosis of additional chronic diseases (Bierman et al., 2007; Blanco-Reina, Ariza-Zafra, Ocaña-Riola, León-Ortíz, & Bellido-Estévez, 2015). For example, long term corticosteroid use can lead to a diabetes mellitus diagnosis (Pilkey, Streeter, Beel, Hiebert, & Li, 2012). Also, fragmented clinical care in persons with cancer and multimorbidity contributes to polypharmacy because multiple physicians prescribe multiple medications concurrently (Feng et al., 2018; Lichtman & Boparai, 2008; Mannucci & Nobili, 2014; Prithviraj et al., 2012).

Polypharmacy, Cancer, and Multimorbidity

Persons with cancer and multimorbidity are at an increased risk for suboptimal therapeutic management and overtreatment (Turner et al., 2020; Turner et al., 2016), in particular, prescribing is a challenge among elderly persons with cancer and multimorbidity (Sharma Loh, Nightingale, Mohile, & Holmes, 2016). A study that included 117 elderly persons aged 65 years and older (mean age of 74.6 years) with newly diagnosed cancer and

multimorbidity with a polypharmacy prevalence rate of 80%, showed the mean number of prescribed and non-prescribed medications were 7.3 and 1.6, respectively (Prithviraj et al., 2012). The authors of this study noted that polypharmacy was significantly associated with drug-drug interactions and adverse drug events in persons with cancer, who were also prescribed chemotherapy.

The clinical management of persons with cancer and multimorbidity is impacted by polypharmacy, especially among older adults. For example, authors of a cohort study that included 229 subjects diagnosed with head and neck cancers and multimorbidity reported a 29.3% prevalence of polypharmacy; it also found that polypharmacy increased clinically significant drug-drug interactions, which led to poor quality of life, health resource utilization, and prolonged hospitalization (Park et al., 2016).

Drug interactions are common among elderly persons with cancer and multimorbidity (Riechelmann et al., 2007; Turner et al., 2014), nearly one-third are exposed to severe drug interactions due to their complex drug regimen (Alkan et al., 2017; Popa, Wallace, Brunello, Extermann, & Balducci, 2014; Prithviraj, et al., 2012; Turner et al., 2016). Studies show that 27% of elderly persons with cancer are at risk for at least one possible drug-interaction as a result of the interplay between prescription drugs, over the counter drugs, and chemotherapy drugs (Hersh, Beldowski, & Hajjar, 2017; Riechelmann et al., 2007). Older adults with cancer and multimorbidity prescribed chemotherapy may have altered drug absorption and drug elimination (Prithviraj et al., 2012; Sharma et al., 2016) which can intensify drug-drug interactions (Maggiore et al., 2014; Tam-McDevitt, 2008; Todd, Williamson, Husband, Baqir, & Mahony, 2013).

Further, individuals with multiple drug therapies have a higher risk for the occurrence of inappropriate medications (Alkan et al., 2017; Hong et al., 2020), drug interactions (Alkan et al., 2017; Stegemann et al., 2010), drug associated injuries (Fried et al., 2014; Olivier et al., 2009; Pardo Cabello et al., 2016), hospitalization (Cascorbi, 2012; Lim et al., 2017), emergency room visits (Hong et al., 2020), and death (Gómez et al., 2015; Jyrkkä, Enlund, Korhonen, Sulkava, & Hartikainen, 2009b; Masnoon et al., 2017; Mazza & Mitchell, 2017; Riechelmann & Del Giglio, 2009; Riechelmann et al., 2007; Safarti et al., 2016; Tan, Suppiah, Bautista, & Malhotra, 2019). In a prospective observational study that included 301 elderly persons 70 years and older with cancer and multimorbidity recruited from 17 different hospitals in Korea, the subjects were prescribed chemotherapy and other medications to manage other chronic diseases, polypharmacy was reported in 45.2% of persons (Hong et al., 2020).

Health Service Utilization as a Result of Cancer, Multimorbidity, and Polypharmacy

The definition of health service utilization varies, and the choice of measurement is dependent on the disease or type of service (Ng et al., 2019), emergency room visits (Billings, & Raven, 2013; Blank et al., 2005; Capp et al., 2016), outpatient visits to clinics (Lin et al., 2007), hospitalizations (Howell, Coory, Martin, & Duckett, 2009; Wright, 2016) and length of stay (Freitas et al., 2012). Additionally, the distribution of health service utilization and health care cost of an individual is often skewed (Calver et al., 2006; Moturu, Johnson, & Liu, 2010; Ng et al., 2019), therefore, defining persons in the top percentiles of health service utilization and cost categories is commonly used (Ng et al., 2019; Wodchis, Austin, & Henry, 2016). For example, the 90th percentile margin is used to identify high health service utilization and high cost users of healthcare (Hayes et al., 2016; Reichard, Gulley, Rasch, & Chan, 2015; Wammes, van der Wees, Tanke, Westert, & Jeurissen, 2018; Wodchis et al., 2016).

Some studies use healthcare cost to determine whether an individual is a high utilizer of healthcare services, and cost can also be considered as a measure of utilization intensity (Diehr, Yanez, Ash, Hornbrook, & Lin, 1999; Heslop, Athan, Gardner, Diers, & Poh, 2005), it gives economic perspective on the use of health services (Ng et al., 2019). High health service utilizers with high healthcare costs are often older, have higher multimorbidity compared to individuals who are not high users (Farjah et al., 2009; Handy et al., 2001; Rais et al., 2013; Rosella et al., 2014; Wammes et al., 2018), and have more severe illness (Reid et al., (2003) which includes persons with cancer (Zulman et al., 2015). Ng et al. (2019) report differences in sociodemographic characteristics and type of chronic diseases in high utilizers, and that utilization patterns are driven by type of disease, disease progression and therapeutic management prescribed.

It is often reported that these high users in the 90th percentile encompass most of the healthcare costs (Reid et al., 2003; Wodchis et al., 2016). In Canada, the cost of cancer management which is mostly as a result of hospital care has steadily increased from 2.9 billion dollars in 2005 to 7.5 billion dollars in 2012 (de Oliveira et al., 2018). An Ontario based study has associated the management of persons with cancer and multimorbidity as a significant cause for hospitalization among individuals with the highest cost of health care (Wodchis et al., 2016). According to Wodchis et al. (2016), cancer is considered as one of the chronic diseases with a large hospital expenditure; the high prevalence of cancer (Ellison & Wilkins, 2012) and high treatment costs (de Oliveira et al., 2013; Mittmann et al., 2014) contribute to its high costs across healthcare services. The health service utilization and associated cost of cancer management increases with the severity of cancer; for example, health care utilization increases with stages I through III of cancer (Mittmann et al., 2012).

The findings of a retrospective cohort study that included persons with lung cancer and multimorbidity 66 years and older, showed that increased health service utilization was a marker for baseline health status, persons who had a higher number of chronic diseases and with greater severity of illness utilized health services more (Farjah et al., 2009). They also noted that increased health service utilization was positively associated with worse health outcomes including long term mortality (Farjah et al., 2009).

Health service utilization is significantly associated with polypharmacy among the elderly with cancer and multimorbidity (Fushiki, Kinoshita, & Tokuda, 2014; Sharma et al., 2016). It is reported that elderly Canadians with polypharmacy have considerable health service utilization compared to elderly Canadians without reported polypharmacy; they utilize emergency room services four times more than Canadian seniors without polypharmacy (Reason et al., 2012).

Prescribed drugs can improve outcomes significantly, however, when multiple drugs are prescribed an adverse drug event is more likely and can cause significant harm (Guthrie, Makubate, Hernandez-Santiago, & Dreischulte, 2015; Pirmohamed et al., 2004). Polypharmacy can be described as the single strongest risk factor for adverse drug events (Balducci et al., 2013) It is shown to be a statistically significant factor in predicting time to first emergency room visit and hospitalizations (Hong et al., 2020), in the elderly it is a common cause for unplanned hospital admissions (Maher et al., 2014).

Adverse drug events have been reported to account for 4 to 10% of all emergency room visits and 5 to 25% of all hospitalizations (Howard et al., 2007; Salazar, Poon, & Nair, 2007). Approximately 30% of persons admitted to hospital experience an adverse drug event while hospitalized (Hohl et al., 2011; Lundkvist & Jönsson, 2004; Mariano et al., 2015; Pirmohamed et

al., 2004). A retrospective study showed that persons with polypharmacy were four times more likely to be hospitalized because of an adverse drug reaction (Marcum, 2012). In a population-based study of ambulatory and emergency room visits, persons with polypharmacy had an 88% increased risk for experiencing an adverse drug event, compared to persons without polypharmacy (Bourgeois et al., 2010).

The co-occurrence of cancer and multimorbidity is associated with significant negative repercussions and long-term effects (Edwards et al., 2014; Jørgensen, Hallas, Friis, & Herrstedt, 2012; Sarfati et al., 2016; Williams et al., 2016), such as decreased quality of life (Marengoni et al., 2011; Yarnall et at., 2017) and increased health service utilization (Fushiki et al., 2014; Salisbury, Johnson, Purdy, Valderas, & Montgomery, 2011; Sharma et al., 2016). Drug interactions are common among persons with cancer and multimorbidity (Hersh et al., 2017; Prithviraj et al., 2012; Riechelmann et al., 2007), they are considered to be a cause of preventable medication-related hospitalizations (Doan et al., 2013; Juurlink, Mamdani, Kopp, Laupacis, & Redelmeier, 2003; Maher et al., 2014; Mallet, Spinewine, & Huang, 2007) and mortality (Blower, de Wit, Goodin, & Aapro, 2005).

Mortality as a Result of Cancer, Multimorbidity, and Polypharmacy

Polypharmacy among persons with cancer and multimorbidity is associated with mortality (Edwards et al., 2014; Elliot et al., 2014; Lund, Borre, Jacobsen, Sørensen, & Nørgaard, 2008; Morishima et al., 2019; Piccirillo, Tierney, Costas, Grove, & Spitznagel, 2004; Søgaard, Thomsen, Bossen, Sørensen, & Nørgaard, 2013; Yarnall et at., 2017), the overall survival of persons with cancer and multimorbidity varies with the prognosis of cancer, stage of cancer, the severity of the concurrent chronic diseases, and the treatment of cancer (Edward et al., 2014; Søgaard et al., 2013).

A retrospective chart review by Elliot et al. (2014) revealed that 38% of persons who were exposed to polypharmacy at the time of admission; after chemotherapy induction and at the time of discharge from hospital, the prevalence of polypharmacy increased to 68%. The authors reported that 19% of persons died within 30 days of induction and 35% died within 60 days; the median overall survival was 6.4 months (Elliot et al., 2014). The authors of the review reported, persons who died within 30 days of chemotherapy induction were taking 5.3 baseline medications, while persons who survived from 30 days or longer were taking 3.9 medications at baseline (Elliot et al., 2014). After adjusting for age, and multimorbidity the authors reported complete remission and greater than 30-day survival was associated with the number of medications taken at the time of chemotherapy induction. In a population-based study by Gómez et al. (2015), that included 5052 elderly persons with cancer and multimorbidity, the results of the study showed that persons with polypharmacy had a higher mortality after a 6.5-year follow-up compared to persons with no polypharmacy, 72.8% and 28.8% respectively.

The association of polypharmacy and mortality in persons with cancer and multimorbidity is a valid concern for clinicians, and more studies are needed (Elliot et al., 2014; Gómez et al., 2015; Jyrkkä et al., 2009b; Pozzi et al., 2010), to fully understand the impact of polypharmacy on vulnerable populations such as older adults with cancer and multimorbidity as well as a wider age group of persons with cancer and multimorbidity.

Research Goals

Cancer is a global health concern, due to its high and increasing incidence. People with cancer also have a high risk of comorbid chronic diseases. Persons with cancer and other chronic diseases require multiple medications to maintain stability of their conditions, which means that

polypharmacy is becoming more common in a population more susceptible to the adverse outcomes associated with polypharmacy.

While the literature adequately describes the occurrence and outcomes of polypharmacy, including among persons with cancer and multimorbidity, the focus is mainly on older adults; and there is sparse literature about younger adults. Therefore, the aim of this study is to examine polypharmacy and its impact among adults 18 years or older with cancer and other chronic diseases. Specifically, it will determine whether the prevalence of polypharmacy differs by age, sex, multimorbidity and type of cancer. The study will also assess the relationship between polypharmacy, health service utilization (i.e., emergency room visits and hospitalization) and death in this group, while controlling for potentially confounding factors.

The findings of this study can contribute to improving the management of polypharmacy in adults 18 years and older with cancer and multimorbidity by Clinical Pharmacists. The assessment of medication profiles by pharmacists to identify exposure to polypharmacy in persons at risk and the implementation of strategies, such as medication therapy management can improve outcomes. The results of this study can also contribute to further studies that assess the appropriateness of polypharmacy in adults 18 years and older with cancer and multimorbidity.

Chapter 3: Methodology and Methods

Methodology

This study sought to determine the prevalence of polypharmacy among adults (18 years or older) with cancer and other comorbidities. Further, to understand the relationship between polypharmacy and health service utilization (i.e., emergency room visits and hospitalization) and death. The specific research questions were:

1. What is the prevalence of polypharmacy among persons with cancer and multimorbidity, and does it vary by age, sex, level of multimorbidity and type of cancer?

2. What is the relationship between polypharmacy prior to cancer diagnosis and health service utilization (i.e., emergency room visits, hospitalizations) and death among persons with cancer and multimorbidity, after taking into account selected confounding factors?

To answer these questions, the study used a quantitative, retrospective longitudinal design, based on provincial health administrative data collected as part of regular practice in Ontario.

Methods

Study Population

This study included Ontarians 18 years and older with a valid Ontario Health Insurance Plan (OHIP) card who were diagnosed with cancer between April 1, 2012 to March 31, 2013 (they may have been diagnosed with one of the selected chronic conditions prior to the cancer diagnosis), and who were covered by the Ontario Drug Benefit (ODB) program. ODB program recipients include all Ontarians 65 years or older. Ontarians who are under the age of 65 will qualify for the ODB program if they are residents of long-term care facilities or homes for special care, persons receiving services under the Home Care Program, Trillium Drug Program recipients, persons receiving special assistance (e.g., Ontario Works, Ontario Disability Support Program), and persons who are eligible for the Special Drugs Program (SDP), regardless of age. It was only as of January 1, 2018, that all persons 24 years and younger who were not covered by a private insurance plan also qualified for the ODB program.

Follow-up data was obtained on the occurrence of selected chronic conditions, service utilization and death until March 31, 2018, or until death if occurring before then. However, persons who died within one year of their cancer diagnosis were excluded. These persons may

have had more severe disease or complications of their chronic diseases and cancer and were

excluded to avoid bias and to minimize reverse causality (Sattar & Preiss, 2017; Yarmolinsky et

al., 2018).

Data Sources

The data in this study are de-identified linked health databases (described below) securely

housed at the Institute of Clinical and Evaluative Services (ICES), that were remotely accessed

and analyzed through their Data and Analytic Virtual Environment (IDAVE).

ICES data covers all Ontarians who receive health services in Ontario and are eligible

for universal health coverage (i.e., almost the entire provincial population).

This study used data from the following databases that were linked using unique encoded

identifiers from ICES: The **National Ambulatory Care Reporting System (NACRS)** provides

data on outpatient hospital visits and community based ambulatory care (physician office visits).

It includes day surgery, emergency room visits, and outpatient clinics. The **Discharge Abstract**

Database (DAD) provides data on hospitalizations in Ontario, including admissions, length of

hospital stays and discharges. The **Ontario Drug Benefit (ODB)** claims database provides

information about drug claims by ODB beneficiaries, such as drug identification number,

number of drugs dispensed, and date dispensed. The **Registered Person Database files (RPDB)**,

provides demographic information (e.g., sex, age, neighbourhood income, rural/urban residence)

for all persons who have ever been issued a valid Ontario health card number. The **Ontario**

Health Insurance Plan (OHIP) claims database, a health plan ran by the government of

Ontario, provides data on claims paid for by OHIP, including hospitalizations and associated

diagnosis, physician visits, medications prescribed while in hospital and some medications in the

ambulatory setting (Government of Ontario, Ministry of Health and Long-Term Care, n.d.). The

Ontario Cancer Registry (OCR), database provides information on all persons living in Ontario who were diagnosed with cancer, that will include date of diagnosis, site of primary cancer and date of cancer death.

Dependent Variables

Beside polypharmacy, as the key dependent variable, three additional outcomes were considered to answer the research questions: emergency room (ER) visits, hospitalizations, and death.

Polypharmacy is the use of medications per year. The number of drugs prescribed within the year prior to cancer diagnosis and within the year following diagnosis was used to determine polypharmacy prior to and following cancer diagnosis. It was defined as the use of five or more drugs (Masnoon et al., 2017; Turner et al., 2016), and was further categorized into 3 groups: <5 drugs (no polypharmacy), 5-9 (polypharmacy), and 10 or more drugs (hyper-polypharmacy).

There were three outcomes of interest: high user of emergency room visits, high user of hospitalizations, and death. The number of emergency room visits and hospitalizations in the year following cancer diagnosis (i.e., average per person-year, within the first year of follow up, i.e. up to March 2014) was examined to determine the number that was equaled to the 90th percentile – which was used to define "high user" (Maddocks et al. 2020; Ng et al., 2019). A percentile value was used because they can be calculated with skewed data, and they are not strongly influenced by extreme values in the distribution (Bornmann, Leydesdorff, & Mutz, 2013; Ng et al., 2019). The number of visits accounting for "high use" of emergency room visits and hospitalizations was 3 or more and 2 or more, respectively. Death was coded as "yes" if the person died between one year after their cancer diagnosis and the end of the study period (i.e., March 31, 2018).

Independent Variables

Table 1 provides detailed information on all study variables.

- Polypharmacy was considered the main predictor variable when analysing the impact on outcomes.

The selection of and controlling for the appropriate confounders is important to ensure that valid associations are made (Skelly, Dettori, & Brodt, 2012). As a result of the literature review the confounders that were controlled for included those with known associations to the study outcomes: age, sex, multimorbidity, type of cancer, stage of cancer. Each of these were recorded at the time of cancer diagnosis.

- Age at the time of diagnosis was further categorized into three groups: 1 = 18 to 44 years, 2= 45 to 64 years, and 3 = 65 years and older. This study also considered separately persons 18 to 44 and 45 to 64 years, who differ from the oldest group in terms of the prevalence of cancer, multimorbidity and health service utilization.

- Sex was measured as male or female.

- Multimorbidity is usually defined as the co-occurrence of two or more chronic diseases (Barnet et al., 2012; Pathirana, & Jackson ,2018). In this study, beside cancer, seventeen chronic diseases were selected, based on previous related research (Koné Pefoyo et al., 2015 & 2021; Roberts et al., 2015): acute myocardial infarction, chronic coronary syndrome, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, asthma, stroke, osteoporosis, dementia, arrhythmias, rheumatoid arthritis, osteoarthritis, anxiety, renal failure, psychotic and mood disorders. Multimorbidity before cancer diagnosis was considered and coded in 4 groups: as none (no conditions), 1, 2, and 3 or more conditions.

- The type of cancer was divided into nine categories which include: breast, colon and rectum, digestive system, female genital, hematological, lung and bronchus, prostate, urinary, and "other".

- The stage of cancer indicates the extent of the cancer severity and informs prognosis. According to the Canadian Cancer Society (n.d.), the stages were measured categorically as; I (the tumor is small and has not grown outside of the primary organ), II and III (the tumor is larger than stage I, or it may have grown outside the primary organ into nearby tissue), and IV (the cancer has spread to a distant site in the body via the blood and lymphatic system) higher stages typically indicate poorer prognosis (Edge & Compton, 2010).

- The mean number of chemotherapy drugs per person prescribed in the year following diagnosis was also considered and categorized as 3 groups to account for < 5 drugs, 5-9 drugs, and 10 or more drugs.

Table 1: Study Variables

Variable	Value	Type
Polypharmacy	<5, 5-9, 10 or more drugs	Categorical
Age group (at time of cancer diagnosis)	1= < 18 years to 44 years	Categorical
	2= 45 years to 64 years	
	3= ≥ 65 years	
Sex	male/female	Categorical
Multimorbidity (among 17 conditions)	0, 1, 2, or 3 or more conditions	Categorical
Cancer type	For example, breast, lung and bronchus, female reproductive system, urinary system, colorectal cancer, prostate, digestive system, and other	Categorical
Cancer stage	I, II, III, IV	Categorical
Chemotherapy drugs	<5, 5-9, 10 or more drugs	Categorical
Hospitalizations	1= high user, i.e., >= 90th percentile (>=2 admissions)	Categorical
	0= Non-high user	
Emergency Room Visits	1= high user, i.e.,>= 90th percentile (>=3 visits)	Categorical
	0= Non-high user	
Death one year after cancer diagnosis, up until March 31, 2018	1= Yes/ 0= No	Categorical

Statistical Analysis

Descriptive statistics (%, mean) were used to characterize the study population regarding demographic characteristics (age, sex), multimorbidity, types of cancer, cancer stage, polypharmacy, and each of the outcome variables (ER visits, hospitalizations, and death).

Hypothesis 1: It was hypothesized that the prevalence of polypharmacy would be different by sex, age, multimorbidity, and cancer type in adults 18 years and older. The prevalence of polypharmacy and hyper-polypharmacy prior to and up to one year following cancer diagnosis was described, and bivariate analysis were conducted to determine if it differed by age, sex, multimorbidity, type of cancer, and stage of cancer. The interaction between multimorbidity level, sex, age, and polypharmacy after a cancer diagnosis was assessed using stratified crosstables. Chi square statistic, a non-parametric (distribution free) test was used to determine if the differences were statistically significant (McHugh, 2013).

Hypothesis 2: It was hypothesized that polypharmacy prior to cancer diagnosis would be significantly associated with increased risk of being a "high user" of health care services (ER visits, hospitalizations) as well as death, even after controlling for the other factors. Multivariate logistic regression was used to quantify the relationship between polypharmacy and each of the three outcomes (i.e., ER visit, hospitalization, and death), while controlling for the other factors (i.e., age, sex, multimorbidity, type of cancer, and stage of cancer (O'Brien & Dunson, 2004; Rijnhart, Twisk, Eekhout, & Heymans, 2019). Adjusted odds ratios and related confidence levels were provided**.**

The statistical analysis software Stata (StataCorp, L.P., 2007) was used to analyze the data. Due to large population sample size, level of significance was fixed at 0.0001 and $p > 0.0001$ was deemed not statistically significant.

Ethical Consideration

This study is part of a larger research study related to cancer and multimorbidity. The researchers involved with these studies have completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics (TCPS 2: CORE). Ethics approval was obtained from ICES (who provided access to the data) and also granted by the Lakehead University Research Ethics Board. An exemption was obtained for this specific thesis project.

As with the larger study, the data used in this study are securely stored in the ICES Data and Analytic Services Environment (IDAVE) databases. Access to the ICES system is restricted to authorized users, and the information regarding persons stored in the administrative databases are deidentified; privacy and security is maintained.

Chapter 4: Results

Demographic and Clinical Characteristics

The study population consisted of 63,828 Ontarians 18 years and older diagnosed with cancer between April 1, 2012 to March 31, 2013. As per the inclusion criteria, all survived for at least one year post cancer diagnosis.

Table 1 shows the study population characteristics overall, as well as by sex and age group. Approximately 49% were male and 51% were female. The mean age was 65.8 years (sd 14.5); males were older than females. Persons 65 years and older represented over 55% of the study population; less than 10% were under the age of 45 years.

Overall, the most prevalent cancer diagnoses were breast, lung and bronchus, and prostate; cancer sites with low prevalence such as brain and other nervous system, oral cavity and pharynx, and skin cancers (excluding basal and squamous cell) were categorized as "other" and represented 19% of the study population. Breast (and female genital cancers) were the two

types most prevalent in females (27.4% and 12.4% respectively); all remaining cancers were more common among males. Hematological cancer and other cancer diagnoses were more prevalent in the youngest group, while lung and bronchus, colon and rectum, digestive system, and urinary system cancers were more prevalent in the oldest group. The oldest group also had lowest prevalence of cancers of the breast and female genitals.

Overall, the stage of cancer was unknown for more than half of the sample. There were more persons with stage I cancer; and this varied by sex and age. Specifically, males had relatively more stage IV diagnoses compared to females. The youngest group had more than double the proportion of people at stage I compared to the oldest group; both older groups had about double the proportion of stage IV cancer compared to the youngest group.

Across the study population, 45.9% had three or more chronic conditions. Differences in multimorbidity before cancer were not statistically significant by sex (χ^2=1.1, p>0.0001), there was a less than a 1% difference between sexes for each level of multimorbidity. Multimorbidity increased significantly with age (χ^2=1.1e+04, p<0.0001) there were over six times as many people in the oldest group with three or more comorbidities compared to the youngest group.

The mean number of chemotherapeutic drugs prescribed in the study population was 7.1, with differences noted by sex and age. Females were prescribed more chemotherapeutic drugs on average compared to males (χ^2=294.6, p<0.0001). With respect to age, the youngest age group were prescribed more chemotherapy drugs on average (χ^2=191.1, p<0.0001).

Table 1. Study population characteristics (persons aged ≥ 18 years who survived at least a year following a cancer diagnosis)

Variables	All N=63,828	Sex		Age		
		Males N=31,238	Females N=32,590	18-44 yrs N=5,080	45-64 yrs N=23,066	65+ yrs N=35,682
Sex[2]						
Males	48.9 %	–	–	35.5 %	47.1 %	52 %
Females	51.1%	–	–	64.5 %	52.9 %	48 %
Age[1]						
18-44 yrs	8 %	5.8 %	10.1 %	–	–	–
45-64 yrs	36.1 %	34.8 %	37.4 %	–	–	–
65+ yrs	55.9%	59.4 %	52.5 %	–	–	–
Mean (SD)	65.8 (14.5)	66.7(13.5)	64.8(15.4)	–	–	–
Cancer type						
Breast cancer[1,2]	14.1 %	0.2 %	27.4 %	17.2 %	17.9 %	11.2 %
Colon & rectum[1,2]	11 %	11.9 %	10.2 %	6.3 %	9.7 %	12.6 %
Digestive system[1,2]	8.9 %	10.4 %	7.5 %	4 %	8.3 %	10.1 %
Female genital [1,2]	6.3 %	0 %	12.4 %	8.4 %	8.2 %	4.8 %
Hematological[1,2]	9.7 %	10.9 %	8.5 %	13.1 %	8.3 %	10.1 %
Lung & bronchus[2]	12.6 %	13.1 %	12 %	1.5 %	9.7 %	16.1 %
Prostate [1,2]	12.1 %	24.7 %	0 %	0.61 %	12.9 %	13.2 %
Urinary system[1,2]	6 %	8.3 %	3.7 %	3.1 %	5.1 %	6.9 %
Other[1,2]	19.3 %	20.4 %	18.3 %	45.9 %	19.9 %	15.1 %
Cancer stage[1,2]						
Stage I	14.1 %	9.4 %	18.5 %	25.2 %	16.2 %	11.1 %
Stage II	12.0 %	13.2 %	10.9 %	10.5 %	12.7 %	11.8 %
Stage III	8.9 %	8.5 %	9.3 %	7.7%	10.2 %	8.2 %
Stage IV	10.9 %	12.5 %	9.4 %	5.8 %	11.1 %	11.5 %
Unknown	54.2 %	56.5 %	51.9 %	50.7%	50 %	57.4 %
Multimorbidity before cancer[2]						
None	13.4 %	13.3 %	13.4 %	39.9 %	19.9 %	5.4 %
1 condition	19.9 %	19.9 %	20 %	33.3 %	26.8 %	13.6 %
2 conditions	20.8 %	20.7 %	20.9 %	16.9 %	22.9 %	20 %
3+ conditions	45.9 %	46.1 %	45.7 %	9.9 %	30.4 %	61.1 %
Mean number of chemo drugs (SD)[1,2]	7.1 (13.1)	6.6 (13.1)	7.6 (13)	10.8 (15.7)	8.5 (15.1)	6.2 (11.6)

[1]Statistically significant difference (p<.0001) by sex
[2]Statistically significant difference (p <.0001) by age

Polypharmacy

Overall, 25.7% had hyper-polypharmacy (10+ drugs) prior to cancer diagnosis, compared to 38.6% post-diagnosis (Table 2). There were significant associations between sex and age and polypharmacy prior to and after diagnosis. Polypharmacy was slightly higher in males before and after a cancer diagnosis. With respect to age, polypharmacy was least common among the youngest group, and increased with age. In fact, hyper-polypharmacy (i.e., 10 or more medications) was present in just over 40% of those 65+ years prior to diagnosis, and more than half post diagnosis. In both younger age groups, prevalence of hyper-polypharmacy more than tripled after diagnosis (i.e., from 2.6% to 12.3% for hose 18-44 years, and from 5.8% to 18.7% among those 45-54 years).

Results show that polypharmacy increased with multimorbidity, both pre and post cancer diagnosis. Prior to cancer diagnosis, the proportion of people with no chronic conditions taking fewer than 5 medications was about three times higher than among those with three or more chronic conditions. This pattern held true post cancer diagnosis, albeit less pronounced (i.e., about two and a half times higher).

Polypharmacy status post cancer diagnosis differed significantly by type of cancer (χ^2=2.4e+03, p<0.0001). Between 20% and one quarter of individuals with breast cancer, colon and rectum cancer, and prostate cancer were taking between 5 and 9 medications; this was true for less than 20% for the remaining cancer types. Hyper-polypharmacy was present in more than half of those with lung and bronchus cancer, and more than 40% of those with cancers in the digestive system, urinary system, colon and rectum, and hematological cancers. The proportion of persons taking fewer than 5 medications steadily decreased with increasing stages of cancer, while hyper-polypharmacy steadily increased (χ^2=1.6e+03, p<0.0001).

Table 2 Association of polypharmacy within one year prior and within one year post cancer diagnosis overall and by age, sex, multimorbidity, cancer type, and cancer stage

Variables	Polypharmacy prior to diagnosis			Polypharmacy post diagnosis		
	<5	5-9	10+	<5	5-9	10+
Overall	53.5 %	20.8 %	25.7 %	42.9 %	18.5 %	38.6 %
Sex[1,2]						
Males	51.6 %	22.3 %	26.1 %	41.6 %	19.3 %	39.2 %
Females	55.4 %	19.3 %	25.3 %	44.2 %	17.7 %	38.1 %
Age[1,2]						
18-44 yrs	94.6 %	2.8 %	2.6 %	78.4 %	9.3 %	12.3 %
45-64 yrs	90 %	4.1 %	5.8 %	70.6 %	10.7 %	18.7 %
65+ yrs	24.1 %	34.1 %	41.8 %	20 %	24.8 %	55.3 %
Multimorbidity before cancer						
None[1,2]	94.4 %	4.6 %	1 %	71.6 %	14.7 %	13.8 %
+1 condition [1,2]	80.7 %	14.9 %	4.4 %	58.3 %	19.5 %	22.3 %
+2 conditions [1,2]	59.4 %	26 %	14.7 %	43.6 %	22.3 %	34.1 %
3+ conditions[1,2]	27.2 %	25.6 %	47.2 %	27.6 %	17.4 %	55 %
Cancer type[2]						
Breast cancer	_	_	_	44.1 %	21.1 %	34.8 %
Colon & rectum	_	_	_	35.9 %	21.0 %	43.2 %
Digestive system	_	_	_	35.5 %	17.0 %	47.5 %
Female genital	_	_	_	52.7 %	15.8 %	31.5 %
Hematological	_	_	_	42.5 %	16.2 %	41.4 %
Lung & bronchus	_	_	_	30.9 %	15.6 %	53.5 %
Prostate	_	_	_	46.5 %	24.3 %	29.2 %
Urinary system	_	_	_	37.3 %	18.6 %	44.1 %
Other				53.9 %	15.9 %	30.3 %
Cancer stage[2]						
Stage I	_	_	_	53.9 %	18 %	28.1 %
Stage II	_	_	_	40.6 %	22.1 %	37.3 %
Stage III	_	_	_	34.3 %	17.5 %	48.3 %
Stage IV	_	_	_	29.7 %	16.6 %	53.8 %
Unknown	_	_	_	44.7 %	18.3 %	37 %

[1]Statistically significant difference pre diagnosis (p <0.0001);
[2]Statistically significant difference post diagnosis (p <0.0001)

Interaction Between MMB, Sex, Age, and Polypharmacy Post Cancer Diagnosis

Figure 1 informs on polypharmacy status post cancer diagnosis by level of

multimorbidity, sex and age. The association with sex and age was significant for each level of

multimorbidity. The combination of old age and highest level of multimorbidity contributes to

the highest prevalence of hyper-polypharmacy, regardless of sex, though the prevalence of

hyper-polypharmacy remains higher for females across all levels of multimorbidity. The lowest

prevalence of hyper-polypharmacy is seen in the youngest age group across levels of

multimorbidity. However, the relationship with sex is less straightforward. Specifically, it

appears that hyper-polypharmacy is lowest among females with no or two conditions, and among

males with either one or three or more conditions.

Figure 1 Polypharmacy increased with MMB by age and sex
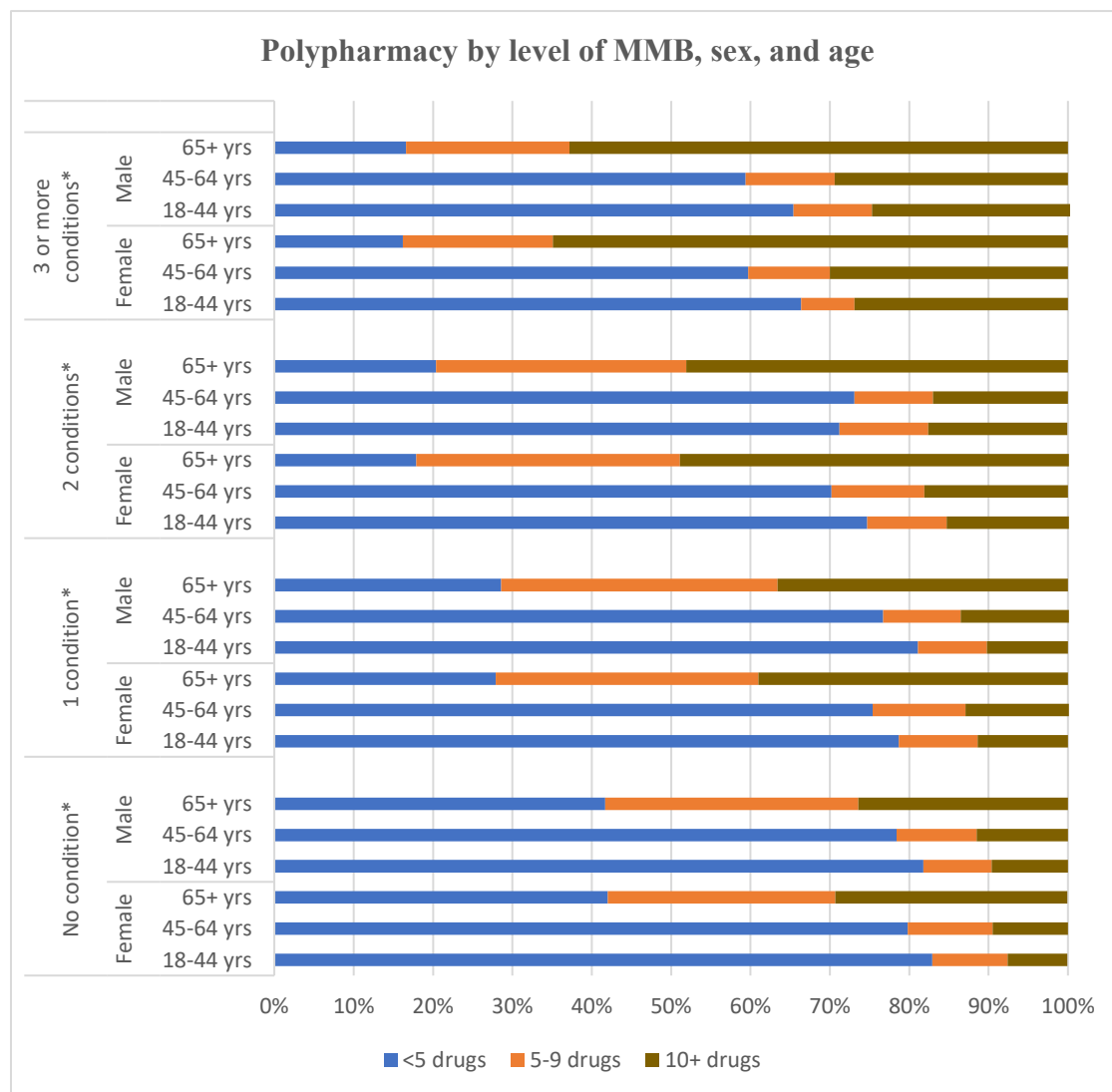
*p<.0001

Impact of Polypharmacy on Health Service Utilisation and Death

Overall, 10.7% of persons in the sample were high users of the ER services and 21.3% high users of hospitalizations in the year after diagnosis. Just over one quarter of the sample (26%) died during follow-up.

ER Services

Table 3 shows that, controlling for other factors, hyper polypharmacy prior to cancer diagnosis was significantly associated with an increased the risk of being a high user of ER services in the year following diagnosis. Persons prescribed 10+ drugs were 34% more likely to be high users than those prescribed less than 5 drugs prior to cancer diagnosis. Other key risk factors associated with increased risk of being a higher user included being male, multimorbidity, certain types of cancer, stage of cancer, and number of chemotherapy drugs, while older age had a lower risk.

Hospitalizations

Table 4 shows that, hyper polypharmacy prior to cancer diagnosis was significantly associated with an increased risk of being in the high user group for hospitalizations after controlling for other factors; however, there was no significant difference between taking 5-9 drugs and fewer than 5 drugs. In addition, persons with 2 and 3 or more additional conditions were 20 % and 41% more likely to be in the higher user group than those with no conditions, respectively. A stage IV diagnosis resulted in an almost 3 times increase in this risk compared to persons at stage I. Other factors associated with increased risk include being male; having cancer in the digestive system, colon and rectum, lung and bronchus, and urinary system; and 5-9 and 10+ of chemotherapy drugs. Older age, breast and prostate cancer were associated with a lower risk.

Table 3 Binary logistic regression model predicting being a higher user of ER services
(N= 63,828)

Variables	OR	99% CI
Polypharmacy prior (ref=<5 drugs)		
5 to 9 drugs	1.13	1.01-1.27
10 or more drugs[*]	1.34	1.20-1.50
Sex (ref=female)		
Male[*]	1.16	1.07-1.26
Age (ref = 18-44 years)		
45-64 years[*]	0.75	0.66-0.86
65 and older[*]	0.50	0.43-0.58
Multimorbidity (ref= no condition)		
1 chronic condition[*]	1.30	1.14-1.48
2 chronic conditions[*]	1.41	1.24-1.62
3+ chronic conditions[*]	1.82	1.60-2.08
Cancer type (ref= other)		
Breast	1.03	0.90-1.17
Colon & rectum	1.07	0.94-1.22
Digestive system (except colon)[*]	1.43	1.25-1.63
Female genital	1.16	0.98-1.37
Hematological	1.05	0.91-1.20
Lung and bronchus	1.12	0.99-1.27
Prostate[*]	0.79	0.68-0.92
Urinary system[*]	1.49	1.28-1.74
Stage of cancer (ref = I)		
II[*]	1.28	1.11-1.48
III[*]	1.41	1.22-1.63
IV[*]	1.50	1.30-1.73
Unknown	1.03	0.91-1.15
Chemotherapy drugs (ref = <5 drugs)		
5-9 drugs[*]	2.43	2.19-2.70
10 or more drugs[*]	3.15	2.87-3.45
cons[*]	0.068	0.057-0.082

[*]$p < 0.0001$

Table. 4 Binary logistic regression model predicting being a high user of hospitalizations (N=63,828)

Variables	OR	99% CI
Polypharmacy prior (ref = <5 drugs)		
5 to 9 drugs	1.02	0.93-1.11
10 or more drugs[*]	1.19	1.09-1.30
Sex (female)		
Male[*]	1.22	1.16-1.30
Age (ref = 18-44 years)		
45-64 years	0.89	0.80-0.99
65 and older[*]	0.74	0.66-0.83
Multimorbidity (ref= no condition)		
1 chronic condition	1.10	1.00-1.21
2 chronic conditions[*]	1.20	1.08-1.32
3+ chronic conditions[*]	1.41	1.28-1.55
Cancer type (ref = other)		
Breast[*]	0.51	0.46-.057
Colon & rectum[*]	1.45	1.32-1.59
Digestive system (except colon)[*]	1.69	1.53-1.87
Female genital	1.16	1.02-1.31
Hematological	1.08	0.97-1.19
Lung and bronchus[*]	1.25	1.14-1.37
Prostate[*]	0.33	0.29-0.37
Urinary system[*]	1.57	1.40-1.76
Stage of cancer (ref = I)		
II[*]	1.66	1.47-1.87
III[*]	2.29	2.04-2.56
IV[*]	2.57	2.30-2.88
Unknown[*]	1.36	1.24-1.50
Chemotherapy drugs (ref = <5 drugs)		
5 to 9 drugs[*]	2.17	1.99-2.36
10 or more drugs[*]	2.27	2.10-2.46
cons[*]	0.13	0.11-0.14

[*]$p < 0.0001$

Death During Follow-up

Table 5 shows the factors associated with death during follow-up. Polypharmacy prior to a cancer diagnosis was significantly associated with an increased risk of death during follow-up. In particular, hyper-polypharmacy had the highest impact, with persons 2 times more likely to die than those taking fewer than 5 drugs prior to their cancer diagnosis.

Being male and increasing age were associated with a higher risk of death; those 65 years and older were three times more likely to die compared to the youngest age group. Having three or more chronic conditions, more advanced stage of cancer, and increasing number of chemotherapeutic drugs were also significantly associated with a higher risk of death. Those with cancer in the lung and bronchus, female genitals, or in the digestive system were most likely to die, whereas those with breast and prostate cancer were least likely to die.

Table 5 Binary logistic regression model predicting death (N=48,577)

Variable	OR	99% CI
Polypharmacy prior (ref= <5 drugs)		
5 to 9 drugs[*]	1.30	1.18-1.42
10 or more drugs[*]	2.02	1.84-2.23
Sex (ref= female)		
Male[*]	1.35	1.26-1.46
Age (18-44 years)		
45-64 years[*]	1.55	1.34-1.80
65 and older[*]	3.08	2.65-3.58
Multimorbidity (ref= no condition)		
1 chronic condition	0.93	0.83-1.04
2 chronic conditions	0.97	0.86-1.08
3+ chronic conditions[*]	1.36	1.21-1.52
Cancer type (ref= other)		
Breast[*]	0.75	0.67-0.85
Colon & rectum	1.10	0.99-1.23
Digestive system (except colon) [*]	3.16	2.77-3.62
Female genital[*]	1.58	1.37-1.83
Hematological	0.95	0.84-1.06
Lung and bronchus[*]	3.90	3.45-4.43
Prostate[*]	0.40	0.35-0.45
Urinary system	1.12	0.98-1.27
Stage of cancer (ref= I)		
II[*]	2.15	1.90-2.44
III[*]	3.76	3.30-4.27
IV[*]	10.47	9.07-12.08
Unknown[*]	2.51	2.26-2.79
Chemotherapy drugs (ref= <5 drugs)		
5-9 drugs[*]	1.69	1.52-1.88
10 or more drugs[*]	2.18	1.99-2.40
cons[*]	0.031	0.026-0.037

[*]$p < 0.0001$

Chapter 5: Discussion

Polypharmacy Prevalence Differed by Levels of Multimorbidity and Age

This study assessed the prevalence of polypharmacy, and the differences by (and interaction between) age, sex, multimorbidity, stage and type of cancer in persons 18+ years and found that each of these played a significant role. The results show that the prevalence was higher in males and older age; it also differed by levels of multimorbidity, which, combined with age had the largest impact.

Finding a relationship between polypharmacy (whether before or after cancer diagnosis) and old age and morbidity was not surprising, as it has been widely reported (for example, Moen et al., 2009; Payne & Avery, 2011), however, differences between younger age groups are not often evaluated.

We observed that on average, persons in the 18-44 age group were prescribed more chemotherapeutic drugs. The literature shows that young and middle-aged adults are more likely prescribed chemotherapy compared to older adults (Manjelievskaia et al., 2017). Older adults with cancer who are frail, have severe multimorbidity, or some other physiologic compromises are less likely prescribed chemotherapy (Balducci, 2007; Given & Given, 2008). This can explain the higher number of chemotherapy drugs in younger adults in our study. Also, the increase in the number of drugs prescribed in younger adults can possibly be due to nonadherence issues. Nonadherence to drug therapy is common in young adults (18+ years) with cancer; studies report that it ranges from 27% to 60% in some types of cancer (Butow et al., 2010; Linder et al., 2019). Failure to comply with recommended drug regimens can result in worsening of disease that may result in additional drug therapy or alternative management in younger adults.

We observed substantial differences in the prevalence of polypharmacy between age groups, and the differences are more pronounced within higher levels of multimorbidity. Polypharmacy is largely associated with multimorbidity; studies report that multimorbidity is prevalent in Ontario and is a significant concern in the elderly as well as persons younger than 65 years (Baek & Shin, 2018; Kone Pefoyo et al., 2015 & 2021). Our study showed that in the 18-44 age group, about one third had at least 1 condition, however the proportion of 3+ conditions was lowest. Older adults (65+ years) had the highest proportion of 3+ conditions, which can explain the higher prevalence of polypharmacy in this age group. Polypharmacy is often required as an adequate form of management in persons with multimorbidity (Aoki et al., 2018; Baek & Shin, 2018; Jorgensen et al., 2011; Mannucci & Nobili, 2014; Schoufour et al., 2018).

In sum, the prevalence of polypharmacy increased as the number of chronic conditions and age increased, and sex did not contribute much to the differences. The prevalence was lowest in females 18-44 years with one condition and highest in females 65+ years with three or more conditions; there was an eight-fold difference in the prevalence of polypharmacy in these two groups. The observed increase within and across multimorbidity levels by age is consistent with other studies (Castioni, Marques-Vidal, Abolhassani., Vollenweider, & Waeber, 2017; Morin, Johnell, Laroche, Fastbom, & Wastesson, 2018; Morio et al., 2019; Ritchie, Kvale, & Fisch, 2011; Slabaugh et al., 2010). Studies that specifically included persons with cancer as a primary diagnosis have also shown that polypharmacy is prevalent among older adults with additional chronic conditions (LeBlanc, McNeil, Kamal, Currow, & Abernethy, 2015; Magnuson et al., 2019; Morio et al., 2019; Nieder, Mannsåker, Pawinski, & Haukland, 2017; Shrestha et al., 2019). Although our study did not determine whether polypharmacy differed by a specific type of chronic condition, previous studies show that varying numbers of drugs are required based on

disease type (Rieckert et al., 2018; Sönnichsen et al., 2016). For example, cardiovascular disease, certain cancers, and pulmonary disease are common among older adults, which, based on clinical guidelines, may require more drugs compared to other conditions to prevent the progression of the disease (Appelros, Stegmayr, & Terént, 2009; Kim, 2011). This can also provide a possible explanation to the combined effect of multimorbidity and age, considering that the distribution of individual diseases varies by age groups.

While our study showed that multimorbidity and age appear to have a greater impact on polypharmacy, the proportion of polypharmacy was comparable between male and females across and within multimorbidity level, regardless of age. We also did not observe a meaningful difference in multimorbidity by sex, which can explain the insubstantial differences in polypharmacy prevalence between men and women. Other studies that included persons with comparable ages to our study group showed variations in the prevalence of polypharmacy and hyper-polypharmacy in men and women at different ages (Hernández-Rodríguez et al., 2020; Hovstadius, Hovstadius, Astrand, & Petersson, 2010). Hernández-Rodríguez et al. (2020) reported in their population-based study that polypharmacy was higher in women, who however, made up a higher proportion of persons 80+ years in the study sample. Also, they reported that the prevalence of hyper polypharmacy was highest in persons 65+ years and was comparable between sexes. Variations and inconsistencies in the prevalence of polypharmacy and hyper-polypharmacy between men and women in our study and other research can be due to the type and number of chronic conditions in men and women (Menditto et al., 2019; Payne et al., 2014), age differences (van den Akker et al., 2019), or even the risk and type of adverse drug reactions experienced (Tatum, Curry, Dunne, Walsh, & Bennett, 2019).

A Diagnosis of Cancer Contributes to Increasing Polypharmacy

The prevalence of polypharmacy was higher after a cancer diagnosis. Particularly, we observed that the prevalence of polypharmacy was highest in persons 65+ years after a cancer diagnosis. Older adults experience many physiological changes that may cause pharmacokinetic and pharmacodynamic changes in drugs, and therefore render them more susceptible to drug therapy problems. These drug therapy related problems often require additional drugs as a form of management (Kadam, 2011; Payne & Avery, 2011) all of which serves to further increase the number of prescribed medications. Overall, the increase in the prevalence of polypharmacy after a cancer diagnosis can be explained by pharmacotherapy being one of the most common treatment modalities for cancer management (Miller et al., 2016; Shrestha, Shrestha, & Khanal, 2019). Most often, cancer therapeutic management is complicated and can cause toxicities that result in more drugs being added to the management plan (Mohamed et al., 2020; Shrestha et al., 2019).

Our study also showed that the prevalence of polypharmacy differs by type of cancer and stage of cancer, where those with lung and bronchus cancer and stage IV cancer had a higher prevalence of hyper polypharmacy. This is consistent with other findings showing that such cancers (Hakozaki et al., 2020; Jorgensen, Herrstedt, Friis, & Hallas, 2011; Lu-Yao et al., 2020) and advanced stages (Kierner, Weixler, Masel, Gartner, & Watzke, 2016) are more often associated with higher prevalence of polypharmacy.

Polypharmacy was Associated with Being a High user of ER and Hospital Services

This study also explored the relationship between polypharmacy, health service use and death. The results showed that, after controlling for other factors, hyper polypharmacy prior to cancer diagnosis was significantly positively associated to being a high user of ER services and hospitalizations one-year post diagnosis. Hyper-polypharmacy (i.e., taking 10+ drugs) was

associated with between 1.2 and 1.3 times higher risk of being a high user of hospitalizations and ER services, respectively. Polypharmacy can be considered a marker for an individual's underlying health status (Fried et al., 2014), which can explain the association with health service utilization. Other population-based studies showed that the risk of ER visits and hospitalizations increased with the number of drugs prescribed in persons with different cancer types (Feng, Higa, Safarudin, Sambamoorthi, & Tan, 2019; Lu-Yao et al., 2020). Our results are also similar to others showing an increase in health care services in general (Dufour et al., 2020; Gutiérrez-Valencia et al., 2017; Hohl, Dankoff, Colacone, & Afilalo, 2001; Maher, Hanlon, & Hajjar, 2014; Resnick et al., 2018; Salvi, Rossi, Lattanzio, & Cherubini, 2017; Wu, Bell, & Wodchis, 2012; Zia, Kamaruzzaman, & Tan, 2015). An adverse drug event can be a consequence of polypharmacy and is one of the main drug related reasons for ER visits and hospitalizations, especially in the elderly (Hong et al., 2020; Maher et al., 2014). Also, about 25% of young adults with significantly higher numbers of prescribed drugs have experienced an adverse drug event (Baek & Shin, 2018; Hernández & Vargas, 2003). Adverse drug events are a common problem among adults with cancer and multimorbidity and are responsible for approximately 10% of ER services (Maher et al., 2014) and about 13% of unplanned hospitalizations (Miranda et al., 2011).

Persons with multimorbidity use more health services than those with no multimorbidity (Canadian Institute for Health Information, 2011), and the risk of health service utilization increases as the number of chronic conditions increase (Mondor et al., 2017). Our study showed persons with 3+ chronic conditions were 82% and 41% more likely to be high users of ER services and hospitalizations, respectively. These findings are similar to other studies where multimorbidity is associated with frequent ER visits and hospitalizations in persons with cancer

(Castillo et al., 2019; Karve et al., 2014; Vyas et al., 2017; Weidner et al., 2018). Castillo et al. (2019) and Hershman et al. (2020) reported that frequent users of ER services were more likely to have more than one chronic condition. Even though the study by Weidner et al. (2018) only included persons with colorectal cancer, their study population included persons 18+ years and their findings showed that persons with more than one chronic condition, who were prescribed chemotherapy were most likely to visit the emergency room. However, contrastingly to our findings they reported that older age was associated with an increased risk.

Our results showed that polypharmacy and multimorbidity were associated with being high users of ER services and hospitalizations, and surprisingly, we found that adults 45+ years and 65+ years were significantly less likely to be "high users" of ER services and hospitalizations, respectively. Older age is a known, common risk factor for both polypharmacy and multimorbidity, and both increase health service utilization (Fano, Chini, Pezzotti, & Bontempi, 2014; Feng et al., 2018; Nie, Wang, Tracy, Moineddin, & Upshur, 2008), and we also know that multimorbidity is common in persons younger than 65 years (Kone Pefoyo et al., 2015 & 2021; Sakib, Shooshtari, St John, & Menec, 2019). As such, our results can be explained by the concept of a "prescribing cascade": drugs prescribed to treat multiple chronic conditions may cause drug adverse effects, additional medications are then prescribed to treat these effects, which further increases the number of drugs and risk of adverse drug events that increase health service utilization (Balducci, Goetz-Parten, & Steinman, 2013; Hersh, Beldowski, & Hajjar, 2017; Ponte, Wachs, Wachs, & Serra, 2017). Our findings regarding older age being associated with reduced odds of being a "high user", can be due to older adults having longer length of hospital stay, which may explain why they are not in and out of hospital as much as younger adults. Also, differences in certain sociodemographic characteristics, such as race and ethnicity,

can determine whether an individual is a "high user" of healthcare services. Quan et al. (2006)

reported that visible minorities had lower hospital admissions compared to other groups.

We found that males were more likely to be high users of health services. A systematic

review by Lash et al. (2017), reported older age and male gender as two significant predictors of

emergency room visits among persons with cancer. Hsu et al. (2018), study findings showed that

slightly more females with cancer utilized emergency room services, however, the difference

was not significant, and the type and stage of cancer was not noted.

Moreover, we found that some types of cancer, advanced stages of cancer, and increased

number of chemotherapy drugs were associated with a higher risk of being a high user of ER

services and hospitalizations, similar to other studies (Barbera & Dudgeon, 2010; Burke et al.,

2011; Karve et al., 2014; Weidner et al., 2018). Certain cancer types and more advanced stages

of cancer determine the frequency of health service utilization. For example, people with lung

cancer have more symptom distress compared to other cancers which may result in more

frequent health service utilization (Feliciana Silva et al., 2020; Karve et al., 2014) and more

advanced stage cancer increases the risk of health service utilization due to their requirement for

supportive management (Feliciana Silva et al., 2020; Yucel, Sukru Erkal, Sinem Akgun, & Serin,

2012). Both the type and stage of cancer impact the number of drugs prescribed, including the

type of chemotherapeutic agents which can potentiate the severity of drug therapy related

problems. Our study results therefore support existing theories regarding polypharmacy and

health service utilization.

Polypharmacy is a Risk Factor for Death Regardless of Age, Sex, and Clinical Characteristics

The risk of death after cancer diagnosis was significantly associated with taking 5+ drugs

prior to cancer diagnosis, with hyper polypharmacy having the greatest impact; those taking 10+

drugs had a twofold increase in the likelihood of death during the study follow-up period. Also, persons 45 years and older, male gender, 3+ chronic diseases, certain types and stage of cancer, and chemotherapy drugs had significant associations.

The risk of drug-disease interactions and drug-drug interactions, increases with the number of drugs prescribed and therefore, mortality rates in persons with cancer increases (Gómez et al., 2015; Jørgensen, Hallas, Land, & Herrstedt, 2010; Mohamed et al., 2020). Polypharmacy is a known prognostic factor in people with cancer and affects overall survival (Hakozaki, Kitadai, & Hosomi, 2019; Mohamed et al., 2020).

We also found that persons with 3+ chronic conditions were 36% more likely to die in the study follow-up period. Similar studies show that persons with multimorbidity who have certain combinations of chronic diseases have a higher risk of death compared to persons with no multimorbidity (Gross et al., 2006). The study by Gross et al. (2006) showed that the combination of diabetes and congestive heart failure, may cause an even higher risk for death. Our study coded multimorbidity into 4 groups according to the number of conditions, whereas Gross et al. (2006) identified specific conditions and grouped them into combinations of diseases.

Our study found that the risk of death was significant in the age group 45-64 years, however, persons 65+ years were 3 times more likely to die compared to persons 18-44 years. We also found that the risk of death was 35% higher in males. A lower risk of death in the 18-44 age group can be explained by a higher proportion of persons in this group being diagnosed at stage 1 cancer, which is a much better prognosis compared to the other age groups. Similarly, the higher risk among males can be explained by a higher proportion of males being diagnosed with stage IV cancer compared to females. There are also age and gender specific differences in the

prevalence and mortality associated with different cancer types (Dorak & Karpuzoglu, 2012; Kim, Lim, & Moon, 2018; Torre et al., 2016; Siegel, Miller, & Jemal, 2016). For example, lung cancer has a very poor prognosis compared to other cancers (Zappa & Mousa, 2016). Our study findings showed a higher prevalence of lung and bronchus cancer in men, and also the risk of death was 90% with this cancer type. Cancer types also differed across age groups in our study. The differences in the risk of death between males and females and by age groups may also be due to the number and type of chronic diseases. Our study did not observe a substantial difference in multimorbidity by sex, but some population-based studies report that males have a higher level of multimorbidity at the time of cancer diagnosis, and poorer prognosis because of this (Janssen-Heijnen et al., 2005; Koppert et al., 2004; Kuijpens et al., 2006).

Overall, a reason for the increased risk of death associated with polypharmacy, multimorbidity, and older age can be the declined ability of the elderly to metabolize drugs, therefore, drug accumulation and the presence of multiple comorbidities can increase the risk of mortality. Our study findings corroborate previous studies, that show polypharmacy has an impact on the risk of death in both young and older adults. There is evidence that a higher number of chronic conditions, sex, stage and type of cancer, and chemotherapy drugs can impact mortality among persons with cancer.

Strengths and Limitations

Strengths

This was a large population-based study that provided reliable results and included all persons covered by the Ontario Drug Benefit (ODB) program during the study period, particularly persons 65+ years, therefore, minimizing selection bias. The health administrative databases provided information on persons diagnosed with all types of cancer and those with multimorbidity for all adults 18+ years at the population level. Most studies that assessed the

prevalence of polypharmacy included mainly older adults with and without cancer, our study has extended the age of the population to include younger adults. Multivariate adjusted analysis was used to control for key confounders identified in the literature.

Limitations

This study population included individuals who have received care through the health care system of Ontario which may have resulted in selection bias (Delgado-Rodríguez & Llorca, 2004; Nohr & Liew, 2018); however, it can be expected that the majority of people with a diagnosis of cancer is likely to have a contact with the health system. Selection bias may have occurred in particular with the 18 to 64 years age group given that not all of them would have been eligible to have their drugs covered by the ODB program. While all people 65 or more are eligible, those younger people covered by the program may represent a special population group, considering that they are residents of long-term care facilities or homes for special care, persons receiving services under the Home Care Program, Trillium Drug Program recipients, persons receiving special assistance (e.g., Ontario Works, Ontario Disability Support Program), and persons who are eligible for the Special Drugs Program (SDP), regardless of age. As of January 1, 2018, persons who are 24 years and younger who are not covered by a private insurance plan also qualify for the ODB program, but this is only a few months at the end of our study period.

Misclassification bias with regards to multimorbidity is also a possible limitation of this study, given that diagnosis and documentation of concomitant diseases may be inaccurate and based on physician practices and the reporting of diseases (Chen, Galfalvy, & Duan, 2013). The difference in the prevalence of polypharmacy in persons with multimorbidity may have been underestimated due to the predefined list of chronic diseases; the study did not include all the possible chronic diseases that may occur in persons with cancer.

This study evaluated only the number of additional chronic conditions, which may be insufficient to understand the extent of polypharmacy related to disease severity among persons with cancer and multimorbidity. Also, we did not know the stage of cancer for about half of the sample, and therefore could not fully understand how stage impacts the prevalence of polypharmacy for the entire study population.

The drug claims of the Ontario Drug Benefit (ODB) program beneficiaries may not include all medications dispensed, for example over the counter preparations and herbal preparations. Thus, there may not be a true representation of the total number of medications dispensed. Inappropriate prescribing was not considered in this study and could not be accurately determined in the context of this thesis. The number of drugs prescribed was provided, however, the therapeutic class, dose and duration of drug therapy could not be determined from the data available. Also, information regarding possible additional confounders was not available, such as alcohol consumption, diet, and physical activity.

Chapter 6: Conclusions

This study examined polypharmacy among both young and old adults 18 years or older with cancer. It found that older adults, males, higher levels of multimorbidity, and specific types of cancer were associated with higher prevalence of polypharmacy. Further, polypharmacy prior to cancer diagnosis was significantly associated with being a high user of ER services and hospitalizations, and of death, even when controlling for other factors. While not necessarily surprising, these remain important findings that add to a growing body of literature in this area. Given that the prevalence of multimorbidity is increasing across age groups, there is need for additional studies that delve further into the nature of polypharmacy – i.e., appropriate vs.

inappropriate, to ensure not only better quality of life for individuals, but also more effective use of the health care system.

While older adults were at increased risk for polypharmacy and multimorbidity, our study showed that these are also present in younger adults. This study showed that younger adults had a significant increase in the prevalence of hyper-polypharmacy after cancer diagnosis and were prescribed more chemotherapeutic drugs compared to adults 65+ years. Certain cancers were shown to be more prevalent in adults 18-44 years old, such as hematological cancer and other types of cancers, and this group had more than twice the proportion of persons with stage I cancer compared to older adults 65+ years. Adults 45+ years and 65+ years old were less likely to be high users of ER services and hospitalizations in the year following cancer diagnosis respectively, and those 45+ years older had a significant association to death during follow-up.

Based on our study findings it is evident that involvement of a multidisciplinary team that includes the input of clinical pharmacists, is needed to monitor and adjust medication lists to reduce or control polypharmacy, and thus ensure optimal outcomes in adults, both young and old, with cancer and multimorbidity.

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