THE LONG-TERM HEALTH EFFECTS AND HEALTHCARE COSTS OF THYROID CANCER SURVIVORS IN POPULATION-BASED COHORT STUDY

by

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ABSTRACT

Thyroid cancer patients have one of the highest 5-year survival rates of any cancer at 98%. It also affects a young population as nearly 67% of thyroid cancer patients are diagnosed before age 55. As these survivors are young and leading long lives after cancer diagnosis and treatment, it is important to understand how their long-term health and finances are affected by thyroid cancer.

Data from the Utah Population Database were utilized to study the long-term health of thyroid cancer survivors. There were 3,706 thyroid cancer survivors and 15,587 matched cancer-free individuals included in the study. All thyroid cancer survivors had increased risks for multiple circulatory health conditions and many other diseases associated with aging. The risks were higher for younger patients diagnosed before age 40 for many outcomes including osteoporosis and diabetes with complications.

Reproductive and pregnancy complications in women diagnosed before age 50 in this population were also studied. Thyroid cancer survivors had increased risks for having multiple health conditions of the female genital organs and multiple health conditions associated with pregnancy. Patients who underwent surgery but did not have radioactive iodine had increased risks for gestational diabetes and missed abortions compared to patients who had both surgery and radioactive iodine treatment.

The Utah All Payer Claims Database (APCD) was utilized to assess the healthcare costs of thyroid cancer patients during the year of their diagnosis and in the following year. On average,

healthcare costs were $19,721.84 in the year of diagnosis and $10,523.88 in the following year. While the total costs decreased, pharmacy costs increased by 112% ($1001.63) between the two years. In the year of surgery, costs were slightly higher for patients who underwent a partial thyroidectomy but significantly lower in the following year when compared those who underwent a total thyroidectomy.

Overall, thyroid cancer survivors have increased risks for long-term health effects and healthcare costs differed by treatment groups. By understanding the trajectory of cancer survivors, health interventions can be put into place to reduce the risk for long-term health effects and thereby reduce healthcare costs.

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CHAPTER 1

INTRODUCTION

Thyroid cancer is the most rapidly increasing cancer in the United States, with an estimated 63,000 new cases in 2016.[1] The 5-year survival rate of thyroid cancer is 98.1%.[2] There are currently over 800,000 thyroid cancer survivors in the United States.[1] Utah has the third highest incidence rate for thyroid cancer in US, with an overall rate of 19.3 per 100,000 population per year.[3] Thyroid cancer affects approximately three times more women than men.[3] Thyroid cancer has a young average age at diagnosis, with nearly two out of three cases being diagnosed under age 55 and the median age of thyroid cancer diagnosis in the US in 2014 being 54 for men and 49 for women.[4,5]

Due to the relatively young age at diagnosis and high survival rates, it is important to understand what long-term health effects may result from the treatment. Common long-term health effects that have previously been reported include salivary and parotid gland disorders, abnormal menstrual cycles, early onset of menopause, dry eye, xerostomia, bone loss, increased heart rate, increased intraventricular thickness, low calcium levels, and headaches.[6-13]

As a result of the increase in thyroid cancer incidence, the costs of thyroid cancer have been rising over time.[13] It was reported that the societal cost of thyroid cancer in 2013 for all patients diagnosed after 1985 was $1.6 billion with 37% of that going to surveillance of survivors.[14] Therefore, understanding the long-term economic costs of thyroid cancer is as

essential as understanding the adverse health effects.

Surgery is the primary treatment and can include removal of all (total thyroidectomy) or part (partial thyroidectomy) of the thyroid with or without removal of regional lymph nodes (lymphadenectomy). Results have shown equivalent survival with either surgical approach, but there is increased controversy for how much removal is appropriate. This controversy is especially apparent in the low to mid risk thyroid cancer patients. Patients often receive radioactive iodine (RAI) following surgery. This may also lead to late health effects. Depending on the thyroid stimulating hormone (TSH) levels and type of surgery, patients may receive TSH suppression therapy or TSH replacement therapy as well.

1.1 Late Effects by Treatment

1.1.1 Radioactive Iodine Treatment

Ten studies reported on the late effects of RAI. Of the 10 studies on RAI, seven of them were cohort studies with the remaining three being cross-sectional studies. Several studies examined the effects of RAI on male and female reproductive organs. Wu et al. observed that RAI was significantly associated with increased time to pregnancy and decreased birth rates for women ages 35-39 in a sample of 25,223.[15] Other reproductive late effects observed include increased risk for induced abortions (both therapeutic and elective) with higher rates of RAI, younger age of menopause, abnormal menstrual cycles, and significant changes in follicle stimulating hormone, luteinizing hormone, and serum inhibin B levels post-therapy in males.[7,8,16]

Other commonly reported late effects with RAI involved the digestive system. Using a cross sectional survey of nearly 2,400 thyroid cancer survivors, Banach et al. reported that 43% of thyroid cancer survivors who had RAI reported xerostomia or dry mouth.[11] Jeong et al. performed salivary gland scintigraphies (SGSs) on 213 patients just prior to RAI and 5 years

later.[6] They observed worsening of overall uptake score and overall ejection fraction in at least 20% of participants showing that about 20% of salivary glands are dysfunctional 5 years after treatment for thyroid cancer.[6] Salivary dysfunction was also reported by Almeida et al. in a study on 182 patients.[1,7] Other common digestive late effects included nausea/vomiting, salivary gland swelling, and taste disturbance.[11]

Zettinig et al. examined the eyes of 88 thyroid cancer patients who had RAI and compared them to sex- and age-matched individuals with no history of radiation.[13] They observed that those who had received RAI were significantly more likely to have symptoms of dry eye, changes in external eye morphology, and altered lacrimal gland function than the controls.[13] However Fard-Esfahani et al. reported that while there is reduction in tear secretion from lacrimal glands after RAI, the symptoms were no greater than those in an unexposed population.[18]

1.1.2 Thyroid Stimulating Hormone Suppression Therapy

There were three studies that examined the impact of TSH suppression therapy. One was a randomized control trial and two were cohort studies. Two studies reported that TSH is significantly associated with bone mineral density loss, especially in postmenopausal women.[9,19] Shargorodsky et al. observed that TSH is significantly associated with increased heart rate and interventricular septum thickness and decreased large and small artery elasticity index and stroke volume in a study on 26 thyroid cancer survivors.[10]

1.1.3 Surgery

Only 1 study reported on the potential late effects of surgery. Self-reported post-surgical complications included low blood calcium levels (39.2%), voice problems (35.6%),

numbness in the neck region (28.9%), restricted neck/shoulder movement (26.8%), and vocal cord palsy (12.1%).[11] Of those who reported these complications, many reported they were still persistent at least 1 year after diagnosis: low blood calcium levels (35.2%), numbness in the neck region (45.3%), restricted neck/shoulder movement (38.8%), and vocal cord palsy (43.0%).[11]

1.1.4 No specific Treatment

There were six studies that did not specify a treatment when examining long-term health effects of thyroid cancer, three cohort and three cross-sectional. Many of the long-term health effects reported were musculoskeletal. Schootman et al. examined self-reported lower-body limitations that included as difficulty/inability to perform at least 1 of 5 activities (walking approximately ¼ mile, walking up and down 10 steps without rest, standing for 2 hours, stooping, crouching, or kneeling, and lifting 10 pounds).[20] They estimated an odds ratio of 2.35 (95% CI=1.19-4.62) when adjusting for sociodemographic factors and health behaviors showing that thyroid cancer survivors are significantly more likely to report lower-body limitations that those who have never had cancer.[20]

Other musculoskeletal long-term health effects observed were leg cramps,[21] pain in joints and muscles,[21,22] lower physical functioning scores when compared to people who never had cancer,[21,22] arthritis and osteoporosis.[12,23] Schultz et al. also observed increasing rates of musculoskeletal effects as years of survivorship increased with nearly 30% of patients who had been survivors for more than 20 years reporting musculoskeletal effects in a sample of 518 thyroid cancer survivors.[12]

1.1.5 Limitations of previous studies

There are several limitations to the studies above. Many of these studies have relatively small sample sizes, with only two of the studies in this review having larger sample sizes than the present study has. Many of these studies were cross-sectional; therefore there was no follow-up. Many of the studies that did have follow-up time had an average follow-up time of less than 2 years. Some of these studies also relied on self-report rather than collecting data from medical records. Most of these studies were narrowly focused on specific long-term health effects building a strong background for what long-term health effects to examine in the present study, but also leaving many long-term health effects unstudied.

1.2 Costs

As incidence rates of thyroid cancer have been continually increasing over time, so have costs.[13] One study using SEER Medicare data reported that cumulative costs for thyroid cancer patients in the first year were $17,669.[24] This was observed in a much older population than was used in the present study. Using the increased rate in thyroid cancer, it has been estimated that costs for the cohort of thyroid cancer patients diagnosed in 2019 will be $2.83 billion and for cohorts diagnosed between 2010 and 2019 the estimated costs associated with diagnosis, treatment, and management are nearly $18.6 billion.[25] Shrime et al. estimated that 20-year costs for thyroid cancer survivors are lower in patients who underwent a total thyroidectomy compared to those who underwent a partial thyroidectomy.[26]

Though costs of thyroid cancer have been studied, much has been estimated from modeling rather than calculated through actual claims data. The study mentioned above that did calculate using claims data did so with a Medicare population, which may not accurately reflect costs for a cancer that has such a young age at diagnosis.

1.3 The Present Study

This study had three aims. The first aim was to examine the risks of aging related diseases and health conditions separately for thyroid cancer survivors who were diagnosed before age 40 and thyroid cancer survivors who were diagnosed age 40 or later. The second aim was to examine the risks of reproductive and pregnancy complications following thyroid cancer for female thyroid cancer survivors diagnosed before the age of 50. Both of these aims utilized the Utah Population Database (UPDB), which contains demographic data as well as statewide medical record data. The final aim of the study was to examine the healthcare costs of thyroid cancer survivors in the year of their diagnosis and the year following. This was done using data from the Utah All Payer Claims Database (APCD) for thyroid cancer survivors who were identified through a linkage to the Utah Cancer Registry (UCR).

This population-based study is one of the largest studies examining the long-term health effects of thyroid cancer with nearly 4,000 thyroid cancer survivors and over 15,000 matched cancer free individuals. This allowed for a high powered study to determine differences between these populations as well as risk factors for the long-term health. The depth of the data for long-term health effects also adds to the study with healthcare data coming from statewide ambulatory surgery and inpatient data, University of Utah healthcare data, and Intermountain Healthcare data. These data did not rely on self-report as many previous large cancer survivor cohorts do.

The linkage of the APCD and the UCR allowed for an in depth study of healthcare costs of thyroid cancer survivors. The majority of cancer cost analysis has used the SEER Medicare data. However as thyroid cancer affects a much younger population than most cancers, SEER Medicare would only allow for a limited population of thyroid cancer patients. Using the Utah APCD allowed for all age groups to be included in the analysis and study by type of

thyroidectomy.

Thyroid cancer survivors are much younger than other adult cancers and have high survival. This is a population that lives a long time after cancer diagnosis. It is important to understand how the health of thyroid cancer survivors is impacted after diagnosis and treatment. As thyroid cancer survivors also have high rates of bankruptcy, it is important to understand the financial toxicity that can affect thyroid cancer patients.[27]

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CHAPTER 2

AGING-RELATED DISEASE RISKS AMONG YOUNG THYROID CANCER SURVIVORS

2.1 Abstract

Thyroid cancer is the most rapidly increasing cancer in the U.S., affects a young population, and has high survival. It is also one of the most common cancers in people under age 40. Younger thyroid cancer patients have been reported to undergo more aggressive treatment and have higher rates of survival. The aim of this study was to examine if thyroid cancer survivors diagnosed at <40 years of age experience greater risks for diseases associated with aging than survivors diagnosed at ≥40 years.

Up to 5 cancer-free individuals were matched to each thyroid cancer survivor diagnosed 1997-2012 based on birth year, sex, birth state, and follow-up time, within the Utah Population Database. Medical records were used to identify disease diagnoses stratified over three time periods: 1-5, >5-10, and 10+ years after cancer diagnosis. Cox proportional hazards models were used to estimate hazard ratios (HR) with adjustment on matching factors, race, BMI at diagnosis, and Charlson Comorbidity Index at time of diagnosis.

There were 3,706 thyroid cancer survivors and 15,587 matched cancer-free individuals (1,365 cases diagnosed <40 years old and 2,341 diagnosed ≥40). Both age groups had increased risks for multiple circulatory health conditions 1-5 years after cancer diagnosis with the young

patients having higher risks (HR=2.25, 99%CI=1.66, 3.05 vs. HR=1.69, 99%CI=1.49, 1.92). For osteoporosis, the younger patients had a higher risk (HR=7.56, 99%CI=1.99, 28.78) than the older population (HR=2.34, 99%CI=1.84, 2.97) 1-5 years after cancer diagnosis, although the difference was not statistically significant.

Thyroid cancer survivors diagnosed at <40 years had increased risks for select diseases associated with aging including hypertension, heart disease, and osteoporosis. As thyroid cancer affects a young population, understanding whether disease risks elevated in thyroid cancer survivors may lead to improved survivorship care.

2.2 Introduction

Thyroid cancer is the most rapidly increasing cancer in the United States with an estimated 64,300 new cases diagnosed in 2015.[1] The 5-year relative survival rate of thyroid cancer is 98.1%.[2] There are currently over 630,000 thyroid cancer survivors in the United States.[3] Utah has the third highest incidence rate (IR) for thyroid cancer in US, with an overall rate of 19.3 per 100,000 population per year.[4] In the United States and in most countries, thyroid cancer affects women more than men.[4] Thyroid cancer also affects a young population, with nearly two out of three cases being diagnosed under age 55. The median age of thyroid cancer diagnosis in the US in 2014 is 54 for men and 49 for women.[5,6]

Aging is associated with a number of conditions including myocardial infarction, arthritis, osteoporosis, glaucoma, and hypertension.[3] Many of these conditions have also been reported as late effects of cancer treatment.[7,8] Cancer treatment has been associated with accelerated aging.[9]

The primary treatment for thyroid cancer is surgery to remove all or part of the thyroid. A significant proportion also receives adjuvant radioactive iodine (RAI) and thyroid stimulating

hormone (TSH) suppression therapy. It is rare for thyroid cancer patients to be treated with chemotherapy except in the case of advanced metastatic disease. Radiation therapy for cancer may be associated with increased risk for cardiovascular diseases, cataracts, hypertension, and eye conditions.[7,8,10] TSH suppressive therapy has been shown to be significantly associated with bone mineral density loss as well as cardiac outcomes such as increased heart rate and decreased stroke volume.[11-13] Other commonly reported conditions or diseases among thyroid cancer survivors include migraine headaches, arthritis, osteoporosis, cataracts, and hearing loss.[14,15]

Thyroid cancer is one of the most common cancers in adolescent and young adults (ages 15-39).[16] Increasing age of thyroid cancer diagnosis has been associated with increased mortality, both overall and cancer specific.[17] Shi et al. reported that overall survival started significantly worsening with diagnosis at age 40 and continued worsening as age at diagnosis increased.[17] It has also been reported that younger patients (< 45 years old at diagnosis) are more likely to undergo a total thyroidectomy and more likely to receive RAI.[18] Young thyroid cancer patients have increased overall survival and cancer specific survival, but may be receiving more aggressive treatment. This younger population is living a long-term and may have increased risks for long-term health effects due to more aggressive treatment

Previous studies on the long-term effects of thyroid cancer survivors have been largely based on small study populations and/or used self-reported data.[13-15] Overall, few studies have investigated multiple disease risks among a large population of both young and elderly thyroid cancer survivors.

The aim of this study was to examine if thyroid cancer survivors diagnosed under the age of 40 experience greater risks of diseases associated with aging than those diagnosed at 40 or older when compared to an age-matched cancer-free population.

2.3 Methods

2.3.1 Data

This cohort was established within the Utah Population Database (UPDB), which links data from the Utah Cancer Registry (one of the original NCI SEER cancer registries), electronic medical records (EMR), statewide healthcare data, voter registration records, residential histories, family history records, and birth and death certificates.[19] The healthcare data from UPDB include ambulatory surgery and inpatient discharge data from the entire state of Utah (1996-2012) as well as linkage to electronic medical records (EMR) data from two of the biggest healthcare providers in Utah, the University of Utah Healthcare (UUHSC) (1994-2015) and Intermountain Healthcare (1995-2015). Nearly 97% of the study population had medical records in at least one of these healthcare data sources with 85.6% having statewide ambulatory surgery and/or inpatient discharge data and 90.4% having UUHSC and/or Intermountain Healthcare EMR data. Treatment data were collected from the Utah Cancer Registry.

Primary thyroid cancer cases identified through the Utah Cancer Registry between 1997-2012 were matched with up to five cancer-free individuals who were concurrently living in Utah at the time of thyroid cancer diagnosis by birth year, sex, and birth state (Utah/not Utah). The last follow-up date is determined by UPDB through last contact with a number of data sources including Driver's License division, Utah birth certificate, death certificate, voter registration, and the Utah Health Department. Death dates are also captured nationwide using genealogy, the Social Security Death Index (nationwide), and the Utah Cancer Registry records.

Participants with thyroid cancer were excluded if the cancer was in situ (n=18) or the cancer stage was unknown/missing (n=101), if they were not living in Utah when they were diagnosed with cancer (n=128), if they had less than 1 year of follow-up time from cancer diagnosis including dying within 1 year (n=243), or an eligible cancer-free individual could not be

matched to them (n=217). Participants in the comparison group were excluded if they had an invasive cancer diagnosis at any time.

All participants were linked to the available healthcare data in the UPDB. The Clinical Classification (CCS) for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) created by the Healthcare Cost and Utilization Project (HCUP) was used to group the ICD-9 codes into clinically meaningful categories.[20] The CCS categorizes ICD-9 codes into four levels, with level 1 being the broadest (e.g. disease of the circulatory system) down to level 4 being the most specific (e.g. atrial fibrillation). A total of 39 aging associated diagnoses were chosen for the current investigation. Of these diagnoses, 20 are associated with the circulatory system. The remaining 19 are associated with the musculoskeletal system (n=9), the nervous system (n=6), and the endocrine system (n=4). Counts for the total number of unique health conditions of the circulatory system and unique health conditions within the other 19 diagnoses were created for each time frame.

Follow-up time was calculated separately for each diagnosis. If the participant had an event for a particular condition, their follow-up time was calculated from thyroid cancer diagnosis date (this was the date of matching for the cancer-free individuals) to the date of diagnosis for that condition. If they were never diagnosed with that condition their follow-up time was calculated from thyroid cancer diagnosis date to their last date known to be alive and residing in Utah.

2.3.2 Statistical Methods

Chi-squared tests were used to assess differences in the demographic characteristics between thyroid cancer survivors and the cancer-free population, as all demographic characteristics were categorized. Demographics related only to cancer survivors (age at

diagnosis, cancer stage, histology, and diagnosis year) were also reported. For analyses of disease risks, the aging related diagnosis was categorized over time: 1 to 5 years, greater than 5 to 10 years, and more than 10 years from cancer diagnosis. Univariate and multivariate Cox proportional hazards models were used to estimate hazard ratios (HR) and 99% confidence intervals (CIs) for all diagnoses across all three time periods. We used 99% confidence intervals to reduce the number of type I errors. We adjusted for matched variables, race, Charlson Comorbidity Index at baseline, and baseline BMI. Hazard ratios between age groups within follow-up periods were tested for statistically significant differences with an alpha of 0.01. The Charlson Comorbidity Index (CCI) was calculated using all medical record data prior to the date of cancer diagnosis and used a measure of baseline health. It was included as a continuous variable in the models. Two of the variables used to calculate the score were excluded (any malignancy and metastatic solid tumor) in order to avoid over adjustment for cancer.[21] Stratified Cox proportional hazards models were run on treatment (surgery only and surgery and radiation). Hazard ratios between treatment groups within age groups and follow-up periods were also tested for statistically significant differences.

The earliest BMI measurement at least 1 year before cancer diagnosis was calculated to assess baseline BMI. Approximately 20% of all participants were missing BMI, and thus we imputed BMI using cancer status, age at diagnosis, sex, race, and Charlson Comorbidity Index as predictors using multiple imputation. We compared Cox regression models including the original BMI variable and the imputed BMI variable to assure that our inferences did not change due to the imputed BMI.

Since the CCS Level 3 and 4 conditions were specific (see Table 2.7), they were analyzed as incident cases only; if a participant had been diagnosed with 1 of the conditions before the time frame for that analyses, they were excluded from that analysis as a prevalent case.

Prevalent cases were identified separately for each follow-up time. Analyses were run separately by thyroid cancer diagnosis age: < 40 years and ≥ 40 years. Using the counts of health problems for the circulatory system and other health problems, risk factor analyses were run for the 1-5-year time frame for the thyroid cancer survivors. The risk factors included treatment (surgery only and surgery with RAI), hormone therapy, cancer stage, age at diagnosis, diagnosis year, sex, BMI at baseline, and Charlson Comorbidity Index at baseline. Cox proportional hazard models were run separately for each risk factor adjusting for potential confounders for that specific risk factor. Those with regional or distant thyroid cancer were combined due to small numbers of distant thyroid cancer. Based on the risk factor analyses, attributable fractions were calculated. All analyses were conducted using SAS (version 9.4).

2.4 Results

The final cohort included 3,706 thyroid cancer survivors and 15,587 cancer-free individuals (Table 2.1). The majority of the study population was white (93.4%) and female (77.7%). The thyroid cancer patients had significantly higher mortality (p-value < 0.0001), higher BMI (p-value < 0.0001), and a family history of thyroid cancer (p-value < 0.0001). As shown in Table 2.2, the number of thyroid cancers increased over time with 13.8% (512) of the survivors being diagnosed between 1997 and 2000 and 37.8% (1,401) being diagnosed in 2011-2012. The median age for diagnosis was 46 years old. Thyroid cancers were diagnosed mostly at localized stage (73.7%) and had a predominant histology of papillary carcinoma (91.9%).

Nearly 37% (1,365) of the thyroid cancer survivors were diagnosed before the age of 40; they were matched to 6,043 cancer-free individuals. Compared to survivors diagnosed at age 40 or older, those diagnosed before the age of 40 were more likely to be female (83.3% vs. 74.7%, p-value <0.0001), have lower BMI at diagnosis (65.4% vs. 43.7%, p-value <0.0001), and be

diagnosed before 2000 (12.3% vs. 8.9%, p-value <0.0001) (Table 2.3). There was also a significant difference in histology (93.9% vs. 90.7% papillary carcinoma, p-value=0.0091) and treatment (54.4% vs. 49.1% receiving surgery and RAI, p-value=0.0068) between the two groups. Treatment data were missing for 56 (1.5%) thyroid cancer survivors.

The proportion of thyroid cancer survivors diagnosed with each of the diseases investigated by age group and follow-up time are shown in Table 2.4. Thyroid cancer survivors diagnosed at age 40 or later had higher proportions of individuals having 1 or multiple circulatory conditions for 1-5 and >5-10 years after thyroid cancer diagnosis than thyroid cancer survivors diagnosed before age 40. While older thyroid cancer survivors were again more likely to have multiple other health conditions in those time frames, they were less likely than younger diagnosed thyroid cancer survivors to have only 1 other health condition. Figure 2.1 shows 10 of the most commonly diagnosed diseases for each time period and age of diagnosis category for the thyroid cancer survivors. Hypertension, back problems, ear conditions and eye conditions were common conditions observed in both younger thyroid cancer survivors and older thyroid cancer survivors. The highest frequency of disease diagnoses was most often after more than 10 years after cancer diagnosis for thyroid cancer survivors diagnosed before age 40 and in the 1-5-year time period for thyroid cancer survivors diagnosed later.

Thyroid cancer survivors diagnosed at <40 years appear to have an increased risk in many circulatory conditions (Table 2.5) when compared to the matched cancer-free population. They had increased risks for multiple health conditions within the circulatory system 1-5 years after cancer diagnosis (HR=2.25, 99% CI=1.66, 3.05 vs. HR=1.69, 99% CI=1.49, 1.92). However, those diagnosed at 40 years or older had higher risks >5-10 and >10 years after thyroid cancer diagnosis. Younger diagnosed thyroid cancer survivors had a higher risk of hypertension than those diagnosed at age 40 or older across all three time periods after cancer diagnosis. The

hypertension risks were higher for thyroid cancer survivors diagnosed at <40 years in the adjusted HR 1-5 years after diagnosis (HR=2.32, 99% CI=1.70, 3.16 vs. HR=1.68, 95% CI=1.50, 1.89). The hazard ratios for younger thyroid cancer survivors were slightly higher, though not significantly higher, in the first time period for diseases of veins and lymphatics (HR=1.60, 99% CI=1.12, 2.28 for younger patients vs. HR=1.58, 95% CI=1.35, 1.85 for older patients). However, the trend switched as time from cancer diagnosis increased; at more than 10 years post-diagnosis the younger population no longer had a significantly increased risk for diseases of the veins and lymphatics (HR=1.10, 95% CI=0.67, 1.81 for younger patients vs. HR=1.49, 95% CI=1.10, 2.01 for older patients).

Overall, thyroid cancer survivors had increased risks for multiple health conditions, but not for only one (Table 2.6). Younger thyroid cancer survivors had a lower risk for multiple health conditions 1-5 years after cancer diagnosis compared to older thyroid cancer survivors (HR=1.51, 99% CI=1.30, 1.75 vs. HR=1.73, 99% CI=1.58, 1.90). However, the risks became closer over time with the younger thyroid cancer survivors having a slightly higher risk more than 10 years after cancer diagnosis (HR=1.48, 99% CI=1.17, 1.87 vs. HR=1.42, 99% CI=1.19, 1.69). The younger thyroid cancer survivors had higher risks for endocrine disorders. The risks for diabetes without complications were higher at both >5-10 and > 10 years after diagnosis (HR=2.19, 99% CI=1.36, 3.51 in younger patients vs. HR=1.36, 99% CI=1.02, 1.80 for older patients). While both age cohorts are at increased risk for ear conditions 1-5 years after thyroid cancer diagnosis, the younger cohort was at a significantly lower risk (HR=1.32, 99% CI=1.06, 1.66 for younger patients vs. HR=1.71, 99% CI=1.46, 1.99 for older patients). The younger thyroid cancer survivors had more than a threefold increased risk in osteoporosis 1-5 years after cancer diagnosis (HR=7.56, 99% CI=1.99, 28.78 compared to HR=2.34, 99% CI=1.84, 2.97).

The risk factor analysis (Table 2.7) showed that the risk for multiple circulatory health

conditions significantly increased with older age at cancer diagnosis, male gender, obese BMI at baseline, and a Charlson Comorbidity Index measure of at least 1 at baseline. The attributable risk fraction showed that age at diagnosis (0.29 for younger survivors and 0.41 older survivors) and baseline Charlson Comorbidity Index (0.26 for younger survivors and 0.32 for older survivors) were the highest contributors for multiple circulatory health conditions. Year of diagnosis had a large attributable risk fraction for those diagnosed younger, but was a very low predictor for those diagnosed older (0.44 vs. 0.01). The findings were similar for risk factors for multiple other health conditions; however treatment was a slightly larger contributor, especially for older thyroid cancer survivors where hormone therapy was associated with a significantly increased risk.

2.5 Discussion

All thyroid cancer survivors had increased risks for multiple health conditions, both within the circulatory system and other health conditions associated with aging. Thyroid cancer survivors diagnosed at <40 years had increased risks for diseases associated with aging such as hypertension, diabetes, and osteoporosis compared to age matched controls, where these diseases are infrequent. Increased age at diagnosis and worse baseline health appeared to be significant contributors to the increased risk of multiple health problems. Several explanations for the significantly elevated risks in the younger diagnosed population exist. It is possible that younger patients received more aggressive therapy than elderly patients, either due to more advanced disease at presentation or due to the clinical perception that they could more readily tolerate aggressive therapy than their older cohort. This was found in our study. A significant difference in the percentage of regional disease between the 2 age groups was noted, with the younger thyroid cancer survivors being more likely to have regional thyroid cancer (28.9% vs.

21.1%). Because the extent of surgical intervention and the use of adjuvant radioactive iodine are frequently guided by the presence and extent of regional disease, this may have contributed to more extensive treatment in the younger cohort. However, the younger cohort was less likely to have distant disease at presentation (1.5% vs. 3.2%) and also had lower attributable fractions for treatment for multiple health problems.

Prolonged exposure to treatment or side effects of treatment may lead to higher rates of the long-term health problems in thyroid cancer survivors, providing another potential explanation for the risks noted. TSH suppression therapy has been reported to be associated with adverse effects including osteoporosis, atrial fibrillation, and increased heart rate.[22] In a study population with a mean age of 61.6, Flynn et al. reported that long-term thyroxine therapy increased risks for cardiovascular disease and osteoporotic fractures, with adjusted hazard ratios of 1.37 (1.17–1.60) and 2.02 (1.55–2.62), respectively.[23] These risk increases are similar to what we observed for diseases of the heart and osteoporosis in the population diagnosed with thyroid cancer ages 40 and older where hormone therapy was associated with an increased risk in multiple health conditions.

In general cancer survivors have higher healthcare utilization than cancer-free individuals in the first few years after diagnosis, which may lead to more health conditions being diagnosed than in the cancer-free population.[24,25] However, younger cancer survivors have been reported to have a disproportionate amount of cancer-related financial problems, which have been linked to delaying or forgoing medical care.[26-28] Further, if cancer survivors are delaying medical care, they may not be getting preventive healthcare, which may lead to health problems that could be prevented such as diabetes and hypertension.

As the diseases studied are diseases of aging, they are more common for both cases and controls in the older group. The difference between the younger thyroid cancer survivors and

the cancer-free individuals may be larger because the diseases are relatively rare in the control group. Due to this, it is possible to infer that the thyroid cancer survivors may have accelerated rates of aging. A large effect is more difficult to find in the older thyroid cancer survivors because these diseases are more common in the cancer-free population.

There are several limitations to this study. First, the study population of Utah is less diverse with low rates of alcohol consumption and smoking. While alcohol and smoking are not risk factors for thyroid cancer, they are risk factors for several of the outcomes studied. We were able to adjust on other proxy factors associated with these factors, such as race, baseline BMI and Charlson Comorbidity Index. Additionally, alcohol drinking and tobacco smoking are unlikely to be associated with increased risk of thyroid cancer, and thus they would not meet the properties of a confounder.[29] Another limitation is the use of ICD-9 codes from medical record data that are likely to contain coding errors. However, we would not expect these errors to be different between the thyroid cancer survivors compared to the cancer-free population. Another limitation is the broad treatment categories. The type of surgery (hemi or total thyroidectomy), dose of RAI, and type of hormone therapy was not given. As this paper was assessing the broad attributable fraction of treatment, it did not detract from the results. Future studies may want to further assess the role of more specific treatments.

The major strength of this study is the population‐based design with approximately 4000 thyroid cancer survivors, nearly 1000 of who have over 10 years of follow-up data available. This large study population allows us to study both common and rare diseases diagnosed over several time periods. Another strength is the amount of medical record data. By having complete EMR data from two of the biggest medical care providers in the state of Utah as well as complete statewide ambulatory surgery and inpatient data, we were able to capture the majority of aging-related diagnosis data available for the study population. This study also does

not rely on self-reported data as many previous studies on the long-term health effects of thyroid cancer have, which gives the advantage of minimizing survival bias as well as recall errors in a cancer survivors cohort.[14,15,30-33]

We may be more likely to capture the healthcare of the cancer survivors than the cancer-free population as the major cancer treatment centers in Utah are within Intermountain Healthcare and UUHSC (including the Huntsman Cancer Institute). Additionally, the cancer survivors are under increased medical surveillance due to their cancer diagnosis and may be diagnosed earlier or more frequently with various diseases. However, we would expect this surveillance to be less intense more than 5 years after cancer diagnosis. We observed increases in risk in these later follow-up times, suggesting that the associations observed in our study are not just due to increased medical surveillance in cancer patients.

While both age groups appear to have significantly increased risk for many diseases associated with aging, in many cases thyroid cancer survivors who were diagnosed at young ages before 40 years appeared to have even higher risks that those diagnosed after 40. Some of the biggest risks were within the cardiovascular, endocrine, and musculoskeletal systems. Further studies are needed to examine how specific cancer treatments play a role in these increased disease risks as well as the interaction between treatment and the risk factors identified in this paper. Future studies are also needed to assess what can be done to reduce the increased risks of these long-term health effects.

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Table 2.1: Characteristics of thyroid cancer survivors and the matched cancer-free cohort

	Thyroid cancer		Comparison group		
	N=3706	%	N=15587	%	P-value
Birth year					
Before 1950	933	25.2	3579	23.0	0.056
1950-1959	853	23.0	3578	23.0	
1960-1969	863	23.3	3764	24.2	
1970-1979	786	21.2	3466	22.2	
1980-1994	271	7.3	1200	7.7	
Sex					
Male	821	22.2	3489	22.4	0.762
Female	2885	77.9	12098	77.6	
Race					
White	3563	96.1	14453	92.7	<0.0001
Nonwhite	137	3.7	683	4.4	
Unknown	6	0.2	451	2.9	
Vital status					
Alive	3453	93.2	14924	95.8	<0.0001
Dead	253	6.8	663	4.3	
Body mass index at baseline **					
<18 kg/m^2	58	1.6	320	2.1	<0.0001
18-24.9 kg/m^2	1915	51.7	8810	56.5	
25-29.9 kg/m^2	1115	30.1	4232	27.2	
30+ kg/m^2	618	16.7	2225	14.3	
Charlson Comorbidity Index at baseline					
0	2518	67.9	12112	77.7	<0.0001
1+	1188	32.1	3475	22.3	
Age attained at the end of follow-up					
<35	226	6.1	1166	7.5	<0.0001
35-44	713	19.2	3254	20.9	
45-54	849	22.9	3775	24.2	
55+	1918	51.8	7392	47.4	
Follow-up period					
1-5	885	23.9	4767	30.6	<0.0001
5-10	1490	40.2	5869	27.7	
10-15	914	24.7	3560	22.8	
15-19	417	11.3	1391	8.9	

* at least 1 year prior to cancer diagnosis for survivor or for the index comparison cohort member

Table 2.2: Clinical characteristics of thyroid cancer survivors

	Thyroid cancer N=3706	%
Diagnosis year		
1997-2000	512	13.8
2001-2004	771	20.8
2005-2008	1022	27.6
2009-2012	1401	37.8
Age at diagnosis		
< 30	500	13.5
30-39	865	23.3
40-49	871	23.5
50-59	772	20.8
60+	698	18.8
Median age = 46		
Cancer stage at diagnosis		
Localized	2732	73.7
Regional	884	23.9
Distant	90	2.4
Histology		
Papillary carcinoma	3405	91.9
Follicular carcinoma	227	6.1
Medullary carcinoma	51	1.4
Anaplastic carcinoma	6	0.2
Other	17	0.5
Treatment		
Surgery only	1732	46.7
Surgery and Radiation	1893	51.1
Other	25	0.7
Missing	56	1.5
Hormone Therapy		
No	2766	74.6
Yes	884	23.9
Missing	56	1.5

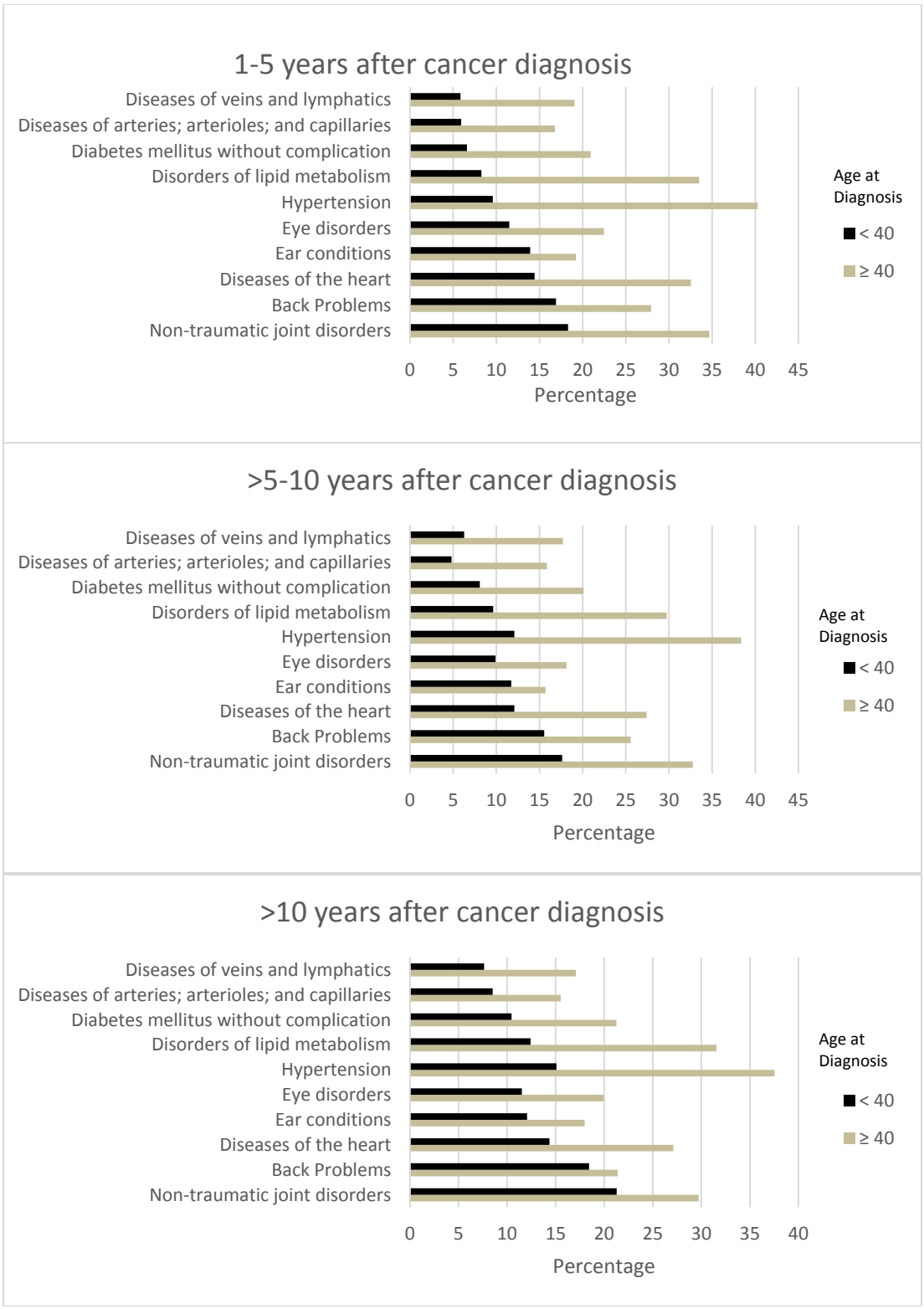

Figure 2.1: Rates of most common outcomes among thyroid cancer survivors

Table 2.3: Characteristics of thyroid cancer survivors by cancer diagnosis age

	Diagnosed under 40		Diagnosed 40 or older		
	N=1,365	%	N=2,341	%	P-value
Birth year					
Before 1950	0	0.0	933	39.9	<0.0001
1950-1959	12	0.9	841	35.9	
1960-1969	338	24.8	525	23.3	
1970-1979	744	54.5	42	21.2	
1980-1994	271	19.9	0	0.0	
Gender					
Male	228	16.7	593	25.3	<0.0001
Female	1,137	83.3	1,748	74.7	
Race					
White	1,314	96.3	2,249	96.1	0.9500
Nonwhite	49	3.6	88	3.8	
Unknown	2	0.2	4	0.2	
Vital status					
Alive	1,345	98.5	2,108	90.1	<0.0001
Dead	20	1.5	233	10.0	
Body mass index at baseline *					
<18 kg/m^2	42	3.1	16	0.7	<0.0001
18-24.9 kg/m^2	892	65.4	1,023	43.7	
25-29.9 kg/m^2	284	20.8	831	35.5	
30+ kg/m^2	147	10.8	471	20.1	
Charlson Comorbidity Index at baseline					
0	1,111	81.4	1,407	60.1	<0.0001
1+	254	18.6	934	39.9	
Follow-up period					
1-5	265	19.4	620	26.5	<0.0001
5-10	536	39.3	954	40.8	
10-15	363	26.6	551	23.5	
15-19	201	14.7	216	9.2	
Diagnosis year					
1997-2000	168	12.3	209	8.9	<0.0001
2001-2004	372	27.3	534	22.8	
2005-2008	485	35.5	883	37.7	
2009-2012	340	24.9	715	30.5	
Cancer stage at diagnosis					
Localized	948	69.5	1,784	76.2	<0.0001
Regional	398	29.2	486	20.8	
Distant	19	1.4	71	3.0	
Histology					
Papillary carcinoma	1,281	93.9	2,124	90.7	0.0091
Follicular carcinoma	66	4.8	161	6.9	
Medullary carcinoma	13	1.0	38	1.6	
Anaplastic carcinoma	0	0.0	6	0.3	
Other	5	0.4	12	0.5	

Table 2.3 Continued

	Diagnosed under 40		Diagnosed 40 or older		
	N=1,365	**%**	**N=2,341**	%	**P-value**
Treatment					
Surgery only	596	43.7	1,136	48.5	0.0068
Surgery and Radiation	743	54.4	1,150	49.1	
Other	5	0.4	20	0.9	
Missing	21	1.5	35	1.5	
Hormone Therapy					
No	1,046	76.6	1,720	73.5	0.0878
Yes	298	21.8	586	25.0	
Missing	21	1.5	35	1.5	

* at least 1 year prior to cancer diagnosis

Table 2.4: Frequencies of outcomes for thyroid cancer survivors by age and time from diagnosis

Diagnosis	CCS Level	1-5 years after cancer diagnosis Percentage		>5-10 years after cancer diagnosis Percentage		>10 years after cancer diagnosis Percentage	
		< 40	≥ 40	< 40	≥ 40	< 40	≥ 40
Circulatory System							
Total number of circulatory system health conditions							
1		16.1	24.6	17.4	20.9	17.0	14.3
2+		9.2	33.3	8.5	31.1	11.9	9.9
Diseases of the circulatory system	1	25.7	59.3	26.4	52.6	29.4	50.9
Hypertension	2	9.6	40.3	12.1	38.3	15.1	37.5
Diseases of the heart	2	14.4	32.6	12.1	27.4	14.4	27.1
Heart valve disorders	3	1.9	7.3	1.5	6.1	3.5	7.8
Congestive heart failure; nonhypertensive	3	0.5	4.4	0.8	4.7	0.9	5.3
Peri-; endo-; and myocarditis; cardiomyopathy	3	0.9	1.8	0.6	1.8	1.1	3.0
Cardiomyopathy	4	0.4	1.1	0.3	1.1	0.7	2.1
Other peri-; endo-; and myocarditis	4	0.6	0.8	0.5	0.8	0.7	1.0
Nonspecific chest pain	3	9.3	17.4	7.0	13.3	8.2	13.7
Pulmonary heart disease	3	0.6	4.0	0.5	4.0	1.6	6.1
Cardiac dysrhythmias	3	6.1	15.9	5.7	13.2	6.2	14.3
Atrial fibrillation	4	0.1	5.1	0.4	5.4	0.5	7.3
Cerebrovascular disease	2	0.7	4.9	1.2	5.1	1.1	5.1
Diseases of arteries; arterioles; and capillaries	2	5.9	16.8	4.8	15.9	8.5	15.5
Peripheral and visceral atherosclerosis	3	0.4	3.1	0.3	3.3	0.9	3.9
Hypotension	4	1.5	3.3	1.1	2.7	2.7	3.5
Diseases of veins and lymphatics	2	5.9	19.1	6.3	17.7	7.6	17.1
Phlebitis; thrombophlebitis and thromboembolism	3	1.5	6.1	2.0	5.3	2.5	5.0
Varicose veins of lower extremity	3	0.9	1.2	0.5	1.3	0.7	1.4
Hemorrhoids	3	3.1	12.1	4.2	11.2	4.1	11.2

Table 2.4 Continued

Diagnosis	CCS Level	1-5 years after cancer diagnosis Percentage		>5-10 years after cancer diagnosis Percentage		>10 years after cancer diagnosis Percentage	
		< 40	≥ 40	< 40	≥ 40	< 40	≥ 40
Other							
Total number of other health conditions							
1		17.4	13.1	12.6	9.9	10.8	11.5
2+		34.9	61.5	34.2	55.9	36.9	30.1
Diabetes mellitus without complication	2	6.6	20.9	8.1	20.1	10.5	21.3
Diabetes mellitus with complications	2	2.2	7.3	2.5	6.4	2.7	7.3
Nutritional deficiencies	2	5.6	10.5	6.5	10.3	8.3	12.4
Disorders of lipid metabolism	2	8.3	33.5	9.6	29.8	12.4	31.6
Delirium dementia and other cognitive disorders	2	0.3	2.3	0.4	2.4	1.8	2.6
Eye disorders	2	11.5	22.5	9.9	18.1	11.5	19.9
Cataract	3	0.4	8.0	0.1	7.2	1.2	9.8
Glaucoma	3	0.2	1.7	0.2	1.4	0.2	2.3
Blindness and vision defects	3	4.8	8.4	3.7	7.4	5.0	7.7
Ear conditions	2	13.9	19.2	11.7	15.7	12.1	18.0
Diseases of the musculoskeletal system and connective tissue	1	37.4	58.4	34.1	52.9	36.9	46.3
Infective arthritis and osteomyelitis	2	0.1	0.9	0.6	0.8	0.7	1.3
Nontraumatic joint disorders	2	18.3	34.7	17.6	32.8	21.3	29.7
Rheumatoid arthritis and related disease	3	1.0	2.0	1.1	2.0	1.4	2.6
Osteoarthritis	3	2.3	19.6	3.9	19.7	4.6	20.2
Back Problems	2	16.9	27.9	15.5	25.6	18.4	21.4
Osteoporosis	2	1.1	9.6	1.3	9.4	1.4	8.6
Pathological fracture	2	0.7	1.5	0.6	1.3	0.9	1.7
Fractures	2	4.5	7.5	3.8	7.5	3.7	8.0

CCS: Clinical Classification Software created by the Healthcare Cost and Utilization Project (HCUP)

Table 2.5: Circulatory system outcomes among thyroid cancer survivors compared to the matched cancer-free cohort, by age at diagnosis and years since cancer diagnosis

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	< 40	≥ 40	< 40	≥ 40
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Diseases of the circulatory system	**1.79 (1.51, 2.14)**	**1.70 (1.54, 1.87)**	**1.58 (1.29, 1.92)**	**1.44 (1.28, 1.62)**
Hypertension	**2.32 (1.70, 3.16)**	**1.68 (1.50, 1.89)**	**1.76 (1.30, 2.37)**	**1.57 (1.36, 1.80)**
Diseases of the heart	**1.76 (1.40, 2.21)**	**1.57 (1.38, 1.77)**	**1.39 (1.06, 1.84)**	**1.35 (1.15, 1.58)**
Heart valve disorders	1.93 (0.99, 3.78)	**1.49 (1.13, 1.95)**	1.28 (0.58, 2.85)	**1.42 (1.02, 1.98)**
Congestive heart failure; nonhypertensive	12.44 (0.97, 158.90)	0.91 (0.65, 1.29)	2.66 (0.64, 11.07)	1.10 (0.73, 1.65)
Peri-; endo-; and myocarditis; cardiomyopathy	**5.58 (1.39, 22.43)**	0.92 (0.54, 1.55)	2.84 (0.74, 10.90)	1.12 (0.59, 2.11)
Cardiomyopathy	5.68 (0.51, 63.47)	0.77 (0.40, 1.48)	3.44 (0.30, 38.98)	0.86 (0.39, 1.91)
Other peri-; endo-; and myocarditis	**7.50 (1.31, 42.84)**	1.41 (0.63, 3.19)	2.94 (0.60, 14.48)	2.10 (0.76, 5.83)
Nonspecific chest pain	**1.82 (1.36, 2.42)**	**1.70 (1.44, 2.01)**	1.18 (0.83, 1.69)	**1.35 (1.07, 1.69)**
Pulmonary heart disease	1.47 (0.45, 4.73)	1.34 (0.93, 1.93)	0.95 (0.26, 3.42)	1.33 (0.87, 2.05)
Cardiac dysrhythmias	**1.79 (1.24, 2.58)**	**1.74 (1.45, 2.08)**	**1.58 (1.05, 2.39)**	**1.40 (1.12, 1.75)**
Atrial fibrillation		1.37 (0.99, 1.88)	1.56 (0.21, 11.77)	**1.43 (1.00, 2.05)**
Cerebrovascular disease	2.26 (0.75, 6.78)	1.20 (0.88, 1.64)	1.52 (0.60, 3.89)	1.19 (0.82, 1.72)
Diseases of arteries; arterioles; and capillaries	**1.77 (1.23, 2.56)**	**1.53 (1.28, 1.82)**	1.26 (0.80, 1.98)	**1.28 (1.04, 1.59)**
Peripheral and visceral atherosclerosis	3.50 (0.38, 32.59)	1.42 (0.93, 2.19)	2.40 (0.25, 22.99)	1.14 (0.70, 1.86)
Hypotension	**2.60 (1.16, 5.86)**	1.26 (0.84, 1.89)	1.98 (0.69, 5.69)	1.06 (0.63, 1.79)
Diseases of veins and lymphatics	**1.60 (1.12, 2.28)**	**1.58 (1.35, 1.85)**	1.37 (0.94, 2.02)	**1.45 (1.20, 1.76)**
Phlebitis; thrombophlebitis and thromboembolism	1.73 (0.82, 3.68)	**1.84 (1.37, 2.47)**	1.80 (0.89, 3.63)	**1.63 (1.14, 2.34)**
Varicose veins of lower extremity	2.64 (0.94, 7.44)	1.27 (0.65, 2.48)	1.07 (0.25, 4.62)	1.13 (0.52, 2.42)
Hemorrhoids	1.31 (0.82, 2.10)	**1.46 (1.21, 1.77)**	1.59 (0.98, 2.55)	**1.33 (1.05, 1.67)**

Table 2.5 Continued

Diagnosis	>10 years after cancer diagnosis	
	< 40	≥ 40
	HR (99% CI)	HR (99% CI)
Diseases of the circulatory system	1.29 (0.99, 1.68)	**1.54 (1.28, 1.85)**
Hypertension	**1.63 (1.13, 2.35)**	**1.46 (1.18, 1.80)**
Diseases of the heart	1.33 (0.92, 1.92)	**1.39 (1.09, 1.77)**
Heart valve disorders	**2.64 (1.17, 5.97)**	1.27 (0.81, 2.01)
Congestive heart failure; nonhypertensive	4.22 (0.65, 27.45)	1.04 (0.59, 1.83)
Peri-; endo-; and myocarditis; cardiomyopathy	4.71 (0.65, 33.89)	1.61 (0.77, 3.40)
Cardiomyopathy	9.93 (0.49, 202.66)	1.54 (0.64, 3.73)
Other peri-; endo-; and myocarditis	5.11 (0.50, 52.52)	1.70 (0.47, 6.20)
Nonspecific chest pain	1.17 (0.74, 1.86)	**1.57 (1.11, 2.21)**
Pulmonary heart disease	2.58 (0.71, 9.37)	**1.89 (1.07, 3.35)**
Cardiac dysrhythmias	1.43 (0.82, 2.51)	**1.44 (1.03, 2.02)**
Atrial fibrillation	5.21 (0.49, 55.92)	**1.94 (1.19, 3.15)**
Cerebrovascular disease	1.18 (0.27, 5.17)	1.28 (0.73, 2.24)
Diseases of arteries; arterioles; and capillaries	1.29 (0.79, 2.12)	1.19 (0.85, 1.65)
Peripheral and visceral atherosclerosis	1.27 (0.27, 5.89)	0.96 (0.48, 1.92)
Hypotension	2.28 (0.81, 6.40)	1.17 (0.60, 2.30)
Diseases of veins and lymphatics	1.10 (0.67, 1.81)	**1.49 (1.10, 2.01)**
Phlebitis; thrombophlebitis and thromboembolism	1.33 (0.53, 3.39)	1.09 (0.60, 1.98)
Varicose veins of lower extremity	1.53 (0.29, 8.13)	1.64 (0.58, 4.62)
Hemorrhoids	0.77 (0.40, 1.50)	**1.55 (1.08, 2.23)**

All HR adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race

*Hazard Ratios between age groups are statistically significant p-value <0.05

Table 2.6: Other outcomes among thyroid cancer survivors compared to the matched cancer-free cohort, by age at diagnosis and years since cancer diagnosis

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	< 40	≥ 40	< 40	≥ 40
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Diabetes mellitus without complications	**2.02 (1.34, 3.04)**	**1.66 (1.39, 1.97)**	**2.20 (1.48, 3.26)**	**1.42 (1.17, 1.73)**
Diabetes mellitus with complications	**2.64 (1.01, 6.93)**	**1.68 (1.24, 2.29)**	2.03 (0.85, 4.85)	1.09 (0.76, 1.58)
Nutritional deficiencies	**4.77 (3.01, 7.56)**	**2.26 (1.80, 2.84)**	**3.10 (1.95, 4.92)**	**1.72 (1.31, 2.25)**
Disorders of lipid metabolism	**2.07 (1.50, 2.85)**	**1.59 (1.41, 1.80)**	**1.78 (1.27, 2.47)**	**1.34 (1.15, 1.56)**
Delirium dementia and amnestic and other cognitive disorders	1.29 (0.21, 7.96)	1.03 (0.66, 1.63)	1.05 (0.22, 4.94)	0.86 (0.51, 1.47)
Eye disorders	**1.73 (1.34, 2.23)**	**1.74 (1.51, 2.02)**	**1.50 (1.10, 2.04)**	**1.26 (1.05, 1.52)**
Cataract	1.58 (0.33, 7.53)	**1.38 (1.09, 1.75)**	0.41 (0.03, 6.38)	1.07 (0.81, 1.43)
Glaucoma	3.39 (0.15, 78.86)	1.31 (0.77, 2.24)		1.00 (0.50, 1.98)
Blindness and vision defects	**1.73 (1.17, 2.57)**	**1.75 (1.38, 2.22)**	1.21 (0.73, 1.98)	**1.54 (1.15, 2.07)**
Ear conditions	**1.32 (1.06, 1.66)**	**1.71 (1.46, 2.00)**	**1.37 (1.03, 1.81)**	**1.50 (1.22, 1.84)**
Diseases of the musculoskeletal system and connective tissue	**1.45 (1.26, 1.67)**	**1.65 (1.51, 1.81)**	**1.34 (1.13, 1.59)**	**1.49 (1.33, 1.68)**
Infective arthritis and osteomyelitis	0.05 (0.00, 20.53)	**2.39 (1.03, 5.55)**	1.57 (0.16, 15.07)	1.33 (0.54, 3.24)
Non-traumatic joint disorders	**1.56 (1.28, 1.90)**	**1.43 (1.28, 1.61)**	**1.38 (1.09, 1.74)**	**1.42 (1.23, 1.63)**
Rheumatoid arthritis and related disease	2.02 (0.83, 4.91)	1.18 (0.72, 1.95)	1.56 (0.59, 4.14)	1.34 (0.75, 2.39)
Osteoarthritis	1.20 (0.67, 2.13)	**1.42 (1.22, 1.66)**	1.36 (0.81, 2.27)	**1.39 (1.16, 1.66)**
Spondylosis; intervertebral disc disorders; other back problems	**1.30 (1.06, 1.60)**	**1.54 (1.35, 1.75)**	**1.27 (1.00, 1.62)**	**1.43 (1.21, 1.68)**
Osteoporosis	**7.56 (1.99, 28.78)**	**2.34 (1.84, 2.97)**	**5.81 (1.75, 19.31)**	**2.19 (1.65, 2.92)**
Pathological fracture	3.26 (0.87, 12.20)	**3.28 (1.70, 6.32)**	3.76 (0.79, 17.91)	1.76 (0.89, 3.50)
Fractures	1.23 (0.83, 1.82)	1.18 (0.93, 1.51)	1.11 (0.68, 1.81)	1.17 (0.88, 1.55)

Table 2.6 Continued

Diagnosis	>10 years after cancer diagnosis	
	< 40	≥ 40
	HR (99% CI)	HR (99% CI)
Diabetes mellitus without complications	**2.19 (1.36, 3.51)**	**1.36 (1.02, 1.80)**
Diabetes mellitus with complications	1.33 (0.52, 3.45)	1.30 (0.77, 2.21)
Nutritional deficiencies	**2.24 (1.31, 3.82)**	**1.86 (1.29, 2.68)**
Disorders of lipid metabolism	**1.74 (1.15, 2.63)**	**1.29 (1.03, 1.62)**
Delirium dementia and amnestic and other cognitive disorders	**4.20 (1.09, 16.17)**	0.53 (0.24, 1.17)
Eye disorders	1.52 (0.99, 2.32)	**1.70 (1.29, 2.26)**
Cataract	3.22 (0.82, 12.68)	**1.51 (1.02, 2.25)**
Glaucoma		**2.39 (1.00, 5.71)**
Blindness and vision defects	1.62 (0.86, 3.05)	**1.59 (1.00, 2.53)**
Ear conditions	1.30 (0.88, 1.92)	**1.78 (1.31, 2.42)**
Diseases of the musculoskeletal system and connective tissue	**1.28 (1.01, 1.62)**	1.16 (0.97, 1.40)
Infective arthritis and osteomyelitis	2.71 (0.35, 21.10)	1.86 (0.57, 6.04)
Nontraumatic joint disorders	1.34 (0.99, 1.82)	1.19 (0.95, 1.48)
Rheumatoid arthritis and related disease	2.62 (0.78, 8.82)	1.63 (0.72, 3.69)
Osteoarthritis	0.96 (0.53, 1.74)	**1.30 (1.00, 1.71)**
Spondylosis; intervertebral disc disorders; other back problems	1.30 (0.93, 1.81)	1.14 (0.88, 1.49)
Osteoporosis	2.10 (0.53, 8.32)	**1.68 (1.09, 2.58)**
Pathological fracture	3.07 (0.58, 16.30)	1.26 (0.45, 3.56)
Fractures	0.86 (0.45, 1.65)	1.09 (0.73, 1.65)

All HR adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race

*Hazard Ratios between age groups are statistically significant p-value <0.05

Table 2.7: Risk factors and attributable fraction for multiple health conditions

	Multiple circulatory system health conditions					
	< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Treatment[1]						
Surgery only		Reference			Reference	
Surgery and RAI	1.08	(0.76, 1.55)	0.04	1.14	(0.98, 1.31)	0.06
Hormone Therapy[1]						
No		Reference			Reference	
Yes	1.01	(0.66, 1.54)	0.00	**1.21**	**(1.02, 1.43)**	0.05
Cancer stage at diagnosis[1]						
Localized		Reference			Reference	
Regional/Distant	0.96	(0.64, 1.44)	0.00	0.99	(0.84, 1.17)	0.00
Age at cancer diagnosis[2]						
< 30		Reference				
30-39	**1.63**	**(1.07, 2.46)**	0.29			
40-49					Reference	
50-59				**1.47**	**(1.20, 1.80)**	0.09
60-69				**2.40**	**(1.94, 2.96)**	0.15
70+				**3.98**	**(3.18, 4.98)**	0.17
Diagnosis year[3]						
1997-2000		Reference			Reference	
2001-2004	1.90	(0.92, 3.91)	0.11	1.00	(0.76, 1.31)	0.00
2005-2008	**2.16**	**(1.07, 4.33)**	0.18	1.02	(0.79, 1.31)	0.01
2009-2012	1.72	(0.86, 3.46)	0.15	0.89	(0.61, 1.01)	0.00
Gender[4]						
Female		Reference			Reference	
Male	1.04	(0.65, 1.66)	0.01	**1.56**	**(1.34, 1.81)**	0.12
Body mass index at baseline[5]						
<18 kg/m^2	1.31	(0.48, 3.60)	0.01	1.14	(0.37, 3.57)	0.00
18-24.9 kg/m^2		Reference				
25-29.9 kg/m^2	1.15	(0.74, 1.80)	0.03	**1.20**	**(1.01, 1.42)**	0.07
30+ kg/m^2	1.48	(0.90, 2.44)	0.06	**1.48**	**(1.22, 1.79)**	0.09
0	Reference	Reference	0	Reference	Reference	0
1+	**2.86**	**(1.98, 4.14)**	1+	**2.86**	**(1.98, 4.14)**	1+

Table 2.7 Continued

	< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Charlson Comorbidity Index[6]						
0		Reference			Reference	
1+	**2.86**	**(1.98, 4.14)**	0.26	**2.19**	**(1.87, 2.55)**	0.32
Number of Cancer[7]						
1		Reference			Reference	
2+	1.05	(0.56, 1.95)	0.00	0.96	(0.75, 1.22)	0.00
			Multiple other health conditions			
Treatment[1]						
Surgery only		Reference			Reference	
Surgery and RAI	0.96	(0.80, 1.15)	0.00	**1.18**	**(1.06, 1.31)**	0.08
Hormone Therapy[1]						
No		Reference			Reference	
Yes	1.17	(0.94, 1.45)	0.04	**1.29**	**(1.14, 1.46)**	0.06
Cancer stage at diagnosis[1]						
Localized		Reference			Reference	
Regional/Distant	0.98	(0.80, 1.20)	0.00	0.98	(0.86, 1.11)	0.00
Age at cancer diagnosis[2]						
< 30		Reference				
30-39	**1.25**	**(1.02, 1.52)**	0.14			
40-49					Reference	
50-59				**1.46**	**(1.28, 1.67)**	0.11
60-69				**1.76**	**(1.51, 2.04)**	0.10
70+				**1.90**	**(1.59, 2.27)**	0.07
Diagnosis year[3]						
1997-2000		Reference			Reference	
2001-2004	1.15	(0.83, 1.59)	0.03	1.21	(0.99, 1.48)	0.03
2005-2008	**1.40**	**(1.03, 1.90)**	0.09	**1.24**	**(1.03, 1.50)**	0.06
2009-2012	1.28	(0.94, 1.72)	0.08	1.13	(0.94, 1.36)	0.05
Gender[4]						
Female		Reference			Reference	
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Male	**0.73**	**(0.56, 0.95)**	0.00	1.06	(0.94, 1.19)	0.01
Body mass index at baseline[5]						
<18 kg/m^2	0.89	(0.50, 1.59)	0.00	0.87	(0.41, 1.83)	0.00
18-24.9 kg/m^2		Reference			Reference	

Table 2.7 Continued

	< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
25-29.9 kg/m^2	0.99	(0.79, 1.25)	0.00	1.12	(0.99, 1.26)	0.04
30+ kg/m^2	1.30	(0.99, 1.71)	0.03	**1.15**	**(1.00, 1.33)**	0.03
Charlson Comorbidity Index[6]						
0		Reference			Reference	
1+	**2.51**	**(2.06, 3.06)**	0.19	**2.01**	**(1.80, 2.25)**	0.25
Number of Cancer[7]						
1						
2+	1.06	(0.77, 1.46)	0.01	0.89	(0.75, 1.08)	0.00

AF: attributable fraction

1: adjusted for age at diagnosis, year of diagnosis, gender, BMI at baseline, CCI at baseline, and race

2: adjusted for BMI at baseline, CCI at baseline, gender, year of diagnosis, stage, histology, and race

3: adjusted for age at diagnosis, BMI at baseline, CCI at baseline, stage and histology

4: not adjusted

5: adjusted on age at diagnosis, CCI at baseline, gender, year of diagnosis, and race

6: adjusted on age at diagnosis, BMI at baseline, gender, year of diagnosis, and race

7: adjusted on treatment, hormone therapy, stage, histology, age at diagnosis, year of diagnosis, gender, BMI at baseline, CCI at baseline, and race

CHAPTER 3

REPRODUCTIVE AND PREGNANCY COMPLICATION RISKS AMONG YOUNG THYROID CANCER SURVIVORS

3.1 Abstract

Thyroid cancer is the most rapidly increasing cancer in the U.S, affects a young, mostly female population, and has high survival. Increased risks for reproductive and pregnancy complications have been previously associated with radioactive iodine (RAI). The aim of this study was to determine if there is an increased risk of reproductive system adverse events or pregnancy complications after women under the age of 50 are diagnosed with thyroid cancer.

Up to 5 female cancer-free individuals were matched to each female thyroid cancer survivor diagnosed before the age of 50 based on birth year, birth state, and follow-up time, within the Utah Population Database. Medical records were used to identify disease diagnoses stratified over three time periods: 0-1, >1-5, and >5-10 years after cancer diagnosis. Cox proportional hazards models were used to estimate hazard ratios (HR) with adjustment on matching factors, race, BMI at diagnosis, and Charlson Comorbidity Index at diagnosis.

There were 1,832 thyroid cancer survivors and 7,921 matched individuals from a general population cohort. Increased risks persisted >5-10 years after cancer diagnosis for menopausal disorders (HR=1.78, 95% CI=1.37, 2.33) and complications related to pregnancy (HR=2.13, 95% CI=1.14, 3.98). Thyroid cancer survivors also had increased risks for gestational

diabetes (HR=2.14, 95% CI=1.23, 3.73) and cervicitis and endocervicitis (HR=2.10, 95% CI=1.10,3.99) >1-5 years after cancer diagnosis. Stratified analyses showed these risks remained increased across different treatment types, including those who had radioactive iodine treatment (RAI).

There were significant risk increases in health outcomes associated with the reproductive system and pregnancy complications. Some of these increased risks which have been previously documented to be associated with RAI, but were increased in patients regardless of treatment.

3.2 Introduction

There are currently more than 630,000 thyroid cancer survivors in the United States.[1] With a 5- year survival rate of more than 98% and the incidence of thyroid cancer rising more rapidly than any other cancer in the United States, the health of thyroid cancer survivors is important to understand.[2] Thyroid cancer affects women more than men with nearly 75% of thyroid cancer cases occurring in women.[3] The median age for thyroid cancer diagnosis in women is 49.[4]

Thyroid cancer treatment typically includes a combination of surgery, radioactive iodine (RAI), and thyroid hormone replacement therapy. It is recommended that women who undergo RAI should wait at least 6 months to become pregnant to reduce the risk of congenital abnormalities, with some experts recommend waiting up to a year.[5,6] Likely due to these recommendations, delayed time to pregnancy has been observed to be associated with patients who receive RAI.[7] Other reproductive effects that have been reported include early menopause, changes in menstrual cycles, and increased rates of spontaneous and induced abortions in the first year after RAI therapy.[8] The rate of miscarriages was increased after surgery for thyroid

cancer, with no significant difference between those who had RAI and those who did not.[9]

The aim of this study was to determine if there is an increased risk of reproductive issues and pregnancy complications in female thyroid cancer survivors under the age of 50.

3.3 Methods

This cohort was established within the Utah Population Database (UPDB), which links data from the Utah Cancer Registry (one of the original NCI SEER cancer registries), electronic medical records (EMR), statewide healthcare data, voter registration records, residential histories, family history records, and birth and death certificates.[10] The healthcare data from UPDB include ambulatory surgery and inpatient discharge data from the entire state of Utah (1996-2012) as well as linkage to electronic medical records (EMR) data from two of the biggest healthcare providers in Utah, the University of Utah Healthcare (UUHSC) (1994-2015) and Intermountain Healthcare (1995-2015). Nearly 97% of the study population had medical records in at least one of these healthcare data sources with 85.6% having statewide ambulatory surgery and/or inpatient discharge data and 90.4% having UUHSC and/or Intermountain Healthcare EMR data. Treatment data were collected from the Utah Cancer Registry.

Primary thyroid cancer cases identified through the Utah Cancer Registry between 1997-2012 were each matched to up to five cancer-free female controls who were living in Utah at the same time by birth year, birth state (Utah/not Utah), and follow-up time. The last follow-up date in UPDB is determined by the most recent among several data sources including drivers license, voter registration, and vital statistics (birth and death certificates, etc.). Death dates are also captured nationwide using genealogy, the Social Security Death Index, and the Utah Cancer Registry records.

Participants with thyroid cancer were excluded if the cancer was in situ (n=18) or the

cancer stage was unknown/missing (n=101), if they were not living in Utah when they were diagnosed with cancer (n=128), if they had less than 1 year of follow-up time from cancer diagnosis (n=243), an eligible cancer-free individual could not be matched to them (n=217), male (n=821), or diagnosed at the age of 50 or older (n=1,053). Participants in the comparison group were not eligible if they had an invasive cancer diagnosis at any time.

All participants were linked to the available healthcare data in the UPDB. The Clinical Classification (CCS) for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) created by the Healthcare Cost and Utilization Project (HCUP) was used to group the ICD-9 codes into clinically meaningful categories.[11] The CCS for ICD-9 CM categorizes the ICD-9 codes into four levels, with level 1 being the broadest (e.g. diseases of the genitourinary system) down to level 4 being the most specific (e.g. pelvic inflammatory disease). A total of 30 outcomes were analyzed which are associated with health conditions of female genital organs (10) and of pregnancy, childbirth, and the puerperium (20). Counts of unique health problems for both female genital organs and pregnancy, childbirth, and the puerperium were created for each time frame. Multiple health problems were counted as having two or more.

Follow-up time was calculated separately for each diagnosis. If the participant had an event for a particular condition, their follow-up time was calculated from cancer diagnosis date (this was the date of matching for the cancer-free individuals) to date of diagnosis for that condition. If they were never diagnosed with that condition their follow-up time was calculated from thyroid cancer diagnosis date to their last date known in Utah or death date.

3.3.1 Statistical Methods

Chi-squared tests were used to assess differences in the demographic characteristics between thyroid cancer survivors and the cancer free population. Demographics related only to cancer survivors (age at diagnosis, cancer stage, histology, diagnosis year, and treatment) were also reported. For analyses of disease risks, the diagnosis was categorized over time: zero to 1 year, 1 to 5 years and 5 to 10 years from cancer diagnosis. Univariate and multivariate Cox proportional hazards models were used to estimate hazard ratios (HR) and 99% confidence intervals (CIs) for all diagnoses across all three time periods. We used 99% confidence intervals to reduce the number of type I errors. We adjusted for race, Charlson Comorbidity Index at baseline, and baseline BMI. The Charlson Comorbidity Index was calculated using all medical record data prior to the date of cancer diagnosis. Two of the variables used to calculate the score were excluded (any malignancy and metastatic solid tumor) in order to avoid over adjustment for cancer.[12]

The earliest BMI measurement at least 1 year before cancer diagnosis was calculated to assess baseline BMI. Approximately 20% of subjects were missing BMI, and thus we imputed BMI using cancer status, age at diagnosis, sex, race, and Charlson Comorbidity Index as predictors using multiple imputation. We compared Cox regression models including the original BMI variable and the imputed BMI variable to assure that our inferences did not change due to the imputed BMI.

Stratified analyses were performed by BMI (normal and overweight/obese), cancer stage (localized and regional/distance), and treatment (surgery only and surgery/RAI). Hazard ratios between stratified groups and follow-up periods were tested for statistically significant differences. All analyses were conducted on SAS (version 9.4).

3.4 Results

The final cohort included 1,832 women diagnosed with thyroid cancer before the age of 50 with 7,921 matched individuals from a general population cohort. The thyroid cancer survivors were significantly more likely to be overweight or obese when compared to the general population cohort (Table 3.1). Women in the matched general cohort were significantly more likely to have children after the date of cancer diagnosis (74.7% vs. 70.9%, p=value=0.001), but not before that time (20.6% vs. 20.9%, p-value=0.776). Thyroid cancer survivors had a significantly higher average age at childbirth (27.6 vs. 26.9, p-value<0.0001).

The median age of cancer diagnosis was 36. The majority of thyroid cancer survivors had papillary cancer (94.2%) and localized cancer (75.1%) as shown in Table 3.2. There were 26 (1.4%) thyroid cancer survivors who did not have treatment data available. Of the 1,806 who did have treatment data available, nearly all (99.7%) had a thyroidectomy (either hemi or total) and just over half (52.4%) received RAI. There were no significant differences in having children before or after cancer diagnosis or average age at childbirth between those who only had surgery and those who had both surgery and RAI (data not shown). Frequencies for all outcomes across all three time periods are shown in Table 3.3.

Table 3.4 shows the overall hazard ratios across all three time periods. In both the first year and >1-5 years after cancer diagnosis, thyroid cancer survivors were significantly more likely to have one or multiple health conditions of female genital organs than the matched general population cohort. That risk went away >5-10 years after cancer diagnosis. There was also significant risk increases for multiple health conditions of pregnancy, childbirth, and the puerperium >1-5 years after cancer diagnosis (HR=1.56, 95% CI=1.28, 1.89). In the first year after cancer diagnosis, thyroid cancer survivors had significant risk increases for menstrual disorders (HR=2.04, 99% CI=1.53, 2.74), ovarian cysts (HR=1.83, 99% CI=1.08, 3.10), and menopausal

disorders (HR=2.15, 99% CI=1.30, 3.56). These risks remained significantly increased through both >1-5 and >5-10 years from cancer diagnosis. In the first year after cancer diagnosis, there were no increased risks for pregnancy complications, and thyroid cancer survivors were significantly less likely to experience complications during labor (HR=0.56, 99% CI=0.33, 0.94) than the general population. There was a significant increase in contraceptive and procreation management with thyroid cancer survivors in both the first year and >1-5 years after cancer diagnosis (HR=1.81, 99%=1.21, 2.71 and HR=1.53, 99% CI=1.17, 1.99, respectively).

Risks for complications related to pregnancy were significantly increased both >1-5 and >5-10 years from cancer diagnosis (HR=1.63, 99% CI=1.36, 1.97 and HR=1.32, 99% CI=1.00, 1.73, respectively). These complications included increased risks for hemorrhage and diabetes or abnormal glucose tolerance during pregnancy, childbirth, and the puerperium. In these time periods, risks for cervicitis and endocervicitis were also significantly increased (HR=2.10, 99% CI=1.10, 3.99 and HR=2.61, 99% CI=1.18, 5.73, respectively). Thyroid cancer survivors were at significantly increased risks compared to the general population cohort for missed abortions (missed miscarriages) >1-5 years after cancer diagnosis (HR=2.16, 99% CI=1.26, 3.73) and for premature rupture of membranes during labor >5-10 years after cancer diagnosis (HR=3.13, 99% CI=1.17, 8.37).

Table 3.5 shows the hazard ratios stratified by localized and regional/distant thyroid cancer. Women diagnosed with regional or distant thyroid cancer had higher risk for developing one health condition of female genital organs >1-5 years after cancer diagnosis (HR=1.57, 95%CI=1.18, 2.09) compared to women diagnosed with local thyroid cancer (HR=1.30, 95% CI=1.10, 1.53). However when examining multiple health conditions, women with localized thyroid cancer had higher risks (HR=1.71, 95% CI=1.37, 2.12 vs. HR=1.42, 95% CI=0.97, 2.07). These risks were not significantly increased for either group >5-10 years after cancer diagnosis.

Women diagnosed with localized thyroid cancer showed significantly increased risks for menstrual disorders, ovarian cysts, and menopausal disorders at both >1-5 and >5-10 years after cancer diagnosis, whereas women with regional or distant thyroid cancer did not show significant increased risks for these in either time period.

Regional and distant thyroid cancer compared to localized thyroid cancer was associated with increased risks for cervicitis and endocervicitis >1-5 years after cancer diagnosis (HR=8.10, 99% CI=1.66, 38.71 vs. HR=1.44, 95% CI=0.67, 3.12, respectively) and hemorrhage during pregnancy, childbirth, or the puerperium >5-10 years after cancer diagnosis (HR=3.23, 99% CI=1.10, 9.48 vs. HR=1.79, 95% CI=0.79, 4.02, respectively). Women with localized thyroid cancer had significantly increased risks for missed abortions >1-5 years after cancer diagnosis (HR=2.26, 99% CI=1.21, 4.20), whereas the risk was not significantly increased for women with regional or distant thyroid cancer (HR=1.87, 95% CI=0.59, 5.92).

Table 3.6 shows the results of the stratified analyses by treatment (surgery only and surgery with RAI). The risks for the number of health conditions were similar between the two treatment groups with women who had both surgery and RAI having slightly higher risks for health conditions of female genital organs and slightly lower risks for multiple health conditions of pregnancy, childbirth, and the puerperium. Thyroid cancer survivors who only had surgery had significant risk increases >1-5 years after cancer diagnosis for diabetes or abnormal glucose tolerance during pregnancy, childbirth, and the puerperium (HR=2.53, 99% CI=1.02, 6.31) and missed abortions (HR=3.08, 99% CI=1.36, 6.99) compared to the matched general population. Women who had both surgery and RAI did not have significant risk increases for either of these (HR=1.98, 95% CI=0.97, 4.06 and HR=1.52, 95% CI=0.70, 3.28, respectively). The thyroid cancer survivors who had both surgery and RAI were more likely to experience premature rupture of membranes during labor (HR=5.17, 99% CI=1.16, 22.99) >5-10 years after cancer diagnosis

compared to those who only had surgery (HR=2.13, 95% CI=0.54, 8.34). Having both surgery and RAI was also associated with higher increased risks in menopausal disorders both >1-5 and >5-10 years after cancer diagnosis than only having surgery.

The stratified hazard ratios by BMI are shown in Table 3.7. Thyroid cancer survivors with normal baseline BMI had lower risks for only 1 health condition of female genital organs >1-5 years after cancer diagnosis than those who were overweight or obese at baseline (HR=1.31, 95% CI=1.10, 1.56 vs. HR=1.53, 95% CI=1.21, 1.93, respectively). Point estimates suggest a difference although the difference was not statistically significant. However, those with normal BMI had higher risks for multiple health conditions (HR=1.74, 95% CI=1.39, 2.18 vs. HR=1.44, 95% CI=1.06, 1.97, respectively). Thyroid cancer survivors with normal BMI at baseline had significantly increased risks for cervicitis and endocervicitis (HR=3.05, 99% CI=1.38, 6.73) >1-5 years after cancer diagnosis, whereas the risk was not significantly increased for those overweight or obese at baseline (HR=1.06, 95%=0.40, 2.84). Thyroid cancer survivors who were overweight or obese at baseline had significant risks for missed abortions (HR=3.93, 99% CI=1.44, 10.72) >1-5 years after cancer diagnosis and premature rupture of membranes during labor (HR=1.31, 99% CI=1.17, 90.49) >5-10 years after cancer diagnosis. These risks were not increased for women with normal BMI at baseline (HR=1.57, 95% CI=0.80, 2.08 and HR=1.36, 95% CI=0.43, 4.25, respectively).

3.5 Discussion

Female thyroid cancer survivors diagnosed before the age of 50 had increased risks for health conditions associated with the reproductive system and pregnancy complications. The majority of the significant risk increases associated with pregnancy were observed >1-5 and >5-10 years from cancer diagnosis. There were very few pregnancy outcomes in the first year after

cancer diagnosis for the thyroid cancer survivors. This may be indicative of patients responding to guidelines and waiting to become pregnant for at least a year after cancer treatment.[5] Thyroid cancer survivors wait longer to have another child after diagnosis, and therefore are older at the time of childbirth, which may account for some of the increases in pregnancy complications.

Both menstrual and menopausal disorders have been previously reported as a late effect of RAI.[13,14] Sioka et al. reported that 31.1% of 45 thyroid cancer survivors reported menstrual cycle irregularities compared to 14.5% of matched controls.[14] These numbers are higher than what we observed (15.1% and 10.3%, respectively, 1-5 years after cancer diagnosis), however we used ICD-9 codes, whereas Sioka et al. used medical records along with interviews asking detailed questions about menstrual irregularities.[14] Other studies have also reported similar rates of increased menstrual irregularities; however they often report them as transient with normal menstrual cycles after the first year.[15,16] We observed significantly increased risks for menstrual disorders across all three time periods, though the risks appeared to be reduced after the first year.

These risks have generally been reported along with RAI and increased doses of RAI.[13,15] RAI also been shown to be associated with an earlier age of menopause.[13,15,17] However, with the stratified treatment we observed increased risks for both menstrual and menopausal disorders across all treatments 1-5 years after cancer diagnosis. These risks appear to be elevated regardless of receiving RAI or not, though the risks for menopausal disorders were elevated in women who had RAI compared to women who only had surgery. The risks for menstrual and menopausal disorders are also significant for women who had localized thyroid cancer, but not for women who had regional or distant thyroid cancer. Part of this may be due

to power of the analysis as there were 1,376 women with localized thyroid cancer and 456 with either regional or distant thyroid cancer.

RAI has also been shown to be associated with increases in miscarriages and abortions; however the increase has not always been reported to be statistically significant.[9,15,18] A literature review of pregnancy outcomes reported that while there was an increased risk of spontaneous and induced abortions in the first year after treatment, but there was little to no long-term risk.[13] Our study observed that there were slightly elevated rates of spontaneous abortions (miscarriages), but there were no significant differences when compared to the general population cohort including in the stratified analyses across all time periods. The rates of induced abortions were very small and the same in both cohorts with only two induced abortions across all three time periods for the thyroid cancer survivors and 13 in the general population cohort. This is lower than other studies have reported in both cases and controls, which may be due to the conservative nature of the state of Utah. While spontaneous and induced abortions were not significantly different between the two cohorts, missed abortions were significantly increased >1-5 years after cancer diagnosis for the thyroid cancer survivors. The stratified analyses showed significantly increased risks for thyroid cancer survivors who had localized thyroid cancer, were overweight or obese at baseline, or received surgery with no RAI.

There was more than a two-fold increased risk of diabetes or abnormal glucose tolerance during pregnancy, childbirth, and the puerperium for thyroid cancer survivors. This includes complications of diabetes mellitus during pregnancy and gestational diabetes. When broken down between these types of diabetes, gestational diabetes accounted for nearly 90% of these cases in both thyroid cancer survivors and the matched general population cohort. In the stratified analyses, women who received surgery only were at significantly increased risks for these complications. Subclinical hypothyroidism in early pregnancy has been to be associated

with increased risk in gestational diabetes.[19] This could warrant the need for higher surveillance for thyroid cancer survivors during early pregnancy for gestational diabetes.

There are several limitations to this study. First, the study population of Utah is less diverse than most areas of the country. However, this allowed for a more homogenous study population. Another limitation is the use of ICD-9 codes from medical record data. There are likely coding errors in these diagnoses codes. However, we would not expect these errors to be different between the thyroid cancer survivors compared to the general population cohort. Another limitation is there is no analysis on hormone therapy. While the majority of the current literature correlates many genital and reproductive late effects with RAI, it is possible that hormone therapy is also playing a role.

The major strength of this study is the population-based design with a large sample size of over 1,800 female thyroid cancer survivors of childbearing age. This large study population allows us to study both common and rare health effects diagnosed over several time periods. Another strength is the amount of medical record data. By having complete EMR data from two of the biggest medical care providers in the state of Utah as well as complete statewide ambulatory surgery and inpatient data, we were able to capture the majority of data available for those in the study. This study also does not rely on self-reported data as many previous studies on the reproductive and pregnancy health effects of thyroid cancer have,[9,14] which gives the advantage of minimizing survival bias as well as recall errors in a cancer survivors cohort.

We may be more likely to capture the healthcare of the cancer survivors than the cancer free population as the major cancer treatment centers in Utah are within IHC and UUHSC (including the Huntsman Cancer Institute). Additionally, the cancer survivors are under increased medical surveillance due to their cancer diagnosis and may be diagnosed earlier or more frequently with various diseases. We would expect this surveillance to be less intense 5+

years after cancer diagnosis. We observed increases in risk in these later follow-up times, suggesting that the associations observed in our study are not just due to increased medical surveillance in cancer patients. In addition, for the health outcomes associated with pregnancy, both thyroid cancer survivors and the women from the general population cohort would have similar medical surveillance during pregnancy.

There were significant risk increases in health outcomes associated with the reproductive system and pregnancy complications. Some of these increased risks such as menstrual disorders, menopausal disorders, and abortions have been documented previously but were mainly associated with RAI treatment. Future studies need to further assess the risks between hormone therapy and genital and reproductive outcomes, in combination with other treatments, for female thyroid cancer survivors of childbearing age.

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Table 3.1: Characteristics of female thyroid cancer survivors diagnosed at < 50 years of age and the general population cohort

	Thyroid cancer		Comparison group		
	N=1832	%	N=7921	%	P-value
Birth year					
1940-1959	282	15.4	1204	15.2	0.972
1960-1979	1316	71.8	5695	71.9	
1980-1994	234	12.8	1022	12.9	
Race					
White	1749	95.6	7375	95.1	0.333
Nonwhite	80	4.4	381	4.9	
Unknown	3		163		
Vital status					
Alive	1805	98.5	7836	98.9	0.147
Dead	27	1.5	85	1.1	
Body mass index at baseline *					
<18 kg/m^2	49	2.7	273	3.5	<0.0001
18-24.9 kg/m^2	1157	63.2	5394	68.1	
25-29.9 kg/m^2	397	21.7	1431	18.1	
30+ kg/m^2	229	12.5	823	10.4	
Had children					
Before cancer diagnosis	382	20.9	1268	20.6	0.776
After cancer diagnosis	1299	70.9	5914	74.7	0.001
Any time	1419	77.5	6457	81.5	<0.0001
	mean	std	mean	std	
Average age at time of first child	24.6	5.1	23.9	4.8	<0.0001
Overall average age of pregnancy	27.6	4.6	26.9	4.4	<0.0001
Average number of children	2.3	1.8	2.4	1.8	0.240
Average number of children before cancer diagnosis	0.4	0.8	0.3	0.8	0.319
Average number of children after cancer diagnosis	2.0	1.7	2.0	1.7	0.097

* at least 1 year prior to cancer diagnosis for them or the cancer survivor they are matched to

Table 3.2: Clinical characteristics of young female thyroid cancer survivors

	Thyroid cancer	
	N=1832	**%**
Diagnosis year		
1997-2000	208	11.4
2001-2005	492	26.9
2006-2010	670	36.6
2011-2012	462	25.2
Age at diagnosis		
< 20	32	1.8
20-29	399	21.8
30-39	706	38.5
40-49	695	37.9
Median age = 36		
Cancer stage at diagnosis		
Localized	1376	75.1
Regional	428	23.4
Distant	28	1.5
Histology		
Papillary carcinoma	1725	94.2
Follicular carcinoma	88	4.8
Medullary carcinoma	13	0.7
Other	6	0.3
Treatment		
Surgery only	854	47.3
Surgery and RAI	947	52.4
Other	5	0.3
Missing	26	

RAI: Radioactive Iodine

Table 3.3: Frequencies of outcomes

Diagnosis	0-1 years after cancer diagnosis		1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Thyroid Cancer Survivors N=1,832 n (%)	General Population Cohort N=7,921 n (%)	Thyroid Cancer Survivors N=1,832 n (%)	General Population Cohort N=7,921 n (%)	Thyroid Cancer Survivors N=1,480 n (%)	General Population Cohort N=5,517 n (%)
Total number of health conditions of female genital organs						
1	273 (14.9)	653 (8.2)*	484 (26.4)	1493 (19.9)*	338 (22.8)	1063 (19.3)*
2+	76 (4.2)	181 (2.3)*	282 (15.4)	746 (9.4)*	205 (13.9)	500 (9.1)*
Total number of health conditions of pregnancy, childbirth, and the puerperium						
1	73 (4.0)	347 (4.4)	128 (7.0)	597 (7.5)	87 (5.9)	285 (5.2)
2+	52 (2.8)	248 (3.1)	261 (14.3)	752 (9.5)*	110 (7.4)	365 (6.6)
Diseases of female genital organs	249 (19.1)	834 (10.5)*	766 (41.8)	2239 (28.3)*	543 (36.7)	1563 (28.3)*
Inflammatory diseases of female pelvic organs	36 (2.0)	104 (1.3)	113 (6.2)	297 (3.8)*	80 (5.4)	211 (3.8)*
Cervicitis and endocervicitis	7 (0.4)	17 (0.2)	27 (1.5)	56 (0.7)*	19 (1.3)	36 (0.7)
Menstrual disorders	124 (6.8)	248 (3.1)*	277 (15.1)	814 (10.3)*	182 (12.3)	493 (8.9)*
Ovarian cyst	35 (1.9)	84 (1.1)*	104 (5.7)	252 (3.2)*	78 (5.3)	204 (3.7)*
Menopausal disorders	41 (2.2)	84 (1.1)*	139 (7.6)	370 (4.7)*	152 (10.3)	354 (6.4)*
Female infertility	10 (0.6)	31 (0.4)	27 (1.5)	75 (1.0)	18 (1.2)	42 (0.8)
Other female genital disorders	128 (7.0)	327 (4.1)*	336 (18.3)	947 (12.0)*	216 (14.6)	577 (10.5)*
Female genital pain and other symptoms	63 (34)	164 (2.1)*	201 (11.0)	550 (6.9)*	133 (9.0)	375 (6.8)*
Other and unspecified female genital disorders	79 (4.3)	195 (2.5)*	199 (10.9)	533 (6.7)*	120 (8.1)	291 (5.3)*
Contraceptive and procreation management, not including sterilization	60 (3.3)	144 (1.8)*	141 (7.7)	384 (4.9)*	73 (4.9)	232(4.2)
Abortion-related disorders	2 (0.1)	23 (0.3)	26 (1.4)	69 (0.9)	7 (0.5)	31 (0.6)

Table 3.3 Continued

Diagnosis	0-1 years after cancer diagnosis		1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Thyroid Cancer Survivors N=1,832 n (%)	General Population Cohort N=7,921 n (%)	Thyroid Cancer Survivors N=1,832 n (%)	General Population Cohort N=1,832 n (%)	Thyroid Cancer Survivors N=7,921 n (%)	General Population Cohort N=1,832 n (%)
Spontaneous abortion	2 (0.1)	22 (0.3)	25 (1.4)	63 (0.8)	6 (0.4)	25 (0.5)
Induced abortion	0 (0.0)	2 (0.0)	1 (0.1)	8 (0.1)	1 (0.1)	3 (0.1)
Complications mainly related to pregnancy	70 (3.8)	334 (4.2)	290 (15.8)	819 (10.3)*	130 (8.8)	406 (7.4)
Ectopic pregnancy	0 (0.0)	6 (0.1)	4 (0.2)	20 (0.3)	3 (0.2)	6 (0.1)
Hemorrhage during pregnancy; abruptio placenta; placenta previa	10 (0.6)	53 (0.7)	49 (2.7)	161 (2.0)	34 (2.3)	71 (1.3)*
Other hemorrhage during pregnancy; childbirth and the puerperium	8 (0.4)	34 (0.4)	45 (2.5)	119 (1.5)*	30 (2.0)	49 (0.9)*
Hypertension complicating pregnancy; childbirth and the puerperium	6 (0.3)	43 (0.5)	26 (1.4)	120 (1.5)	20 (1.4)	64 (1.2)
Preeclampsia and eclampsia	3 (0.2)	21 (0.3)	10 (0.6)	45 (0.6)	14 (1.0)	35 (0.6)
Early or threatened labor	8 (0.4)	35 (0.4)	57 (3.1)	175 (2.2)	16 (1.1)	46 (0.8)
Prolonged pregnancy	3 (0.2)	23 (0.3)	23 (1.3)	94 (1.2)	7 (0.55)	51 (0.9)
Diabetes or abnormal glucose tolerance	6 (0.3)	23 (0.3)	37 (2.0)	71 (0.9)*	15 (1.0)	33 (0.6)
Other complications of pregnancy	64 (3.5)	239 (3.0)	268 (14.6)	641 (8.1)*	119 (8.0)	323 (5.9)*
Missed abortion	4 (0.2)	20 (0.3)	35 (1.9)	72 (0.9)*	13 (0.9)	46 (0.8)
Other and unspecified complications of pregnancy	61 (3.3)	187 (2.4)	252 (13.8)	537 (6.8)*	113 (7.6)	283 (5.1)*
Fetal distress and abnormal forces of labor	5 (0.3)	25 (0.3)	17 (0.9)	110 (1.4)	6 (0.4)	30 (0.5)
Premature rupture of membranes	0 (0.0)	16 (0.2)	12 (0.7)	45 (0.6)	13 (0.9)	21 (0.4)
Complications during labor	28 (1.5)	221 (2.8)*	175 (9.6)	617 (7.8)	82 (5.5)	272 (4.9)
Normal delivery	8 (0.4)	80 (1.0)	60 (3.3)	254 (3.2)	23 (1.8)	98 (1.8)

*Chi-squared or Fisher's exact p-value <0.01

Table 3.4: Reproductive and pregnancy outcomes among thyroid cancer survivors compared to the general population cohort, by years since cancer diagnosis

Diagnosis	0-1 years after cancer diagnosis HR (99% CI)	1-5 years after cancer diagnosis HR (99% CI)	5-10 years after cancer diagnosis HR (99% CI)
Total number of health conditions of female genital organs			
1	**1.81 (1.49,2.19)**	**1.36 (1.18, 1.56)**	1.07 (0.76, 1.50)
2+	**1.81 (1.26, 2.59)**	**1.63 (1.35, 1.96)**	1.12 (0.64, 1.97)
Total number of health conditions of pregnancy, childbirth, and the puerperium			
1	0.92 (0.65, 1.28)	0.86 (0.67, 1.12)	0.61 (0.21, 1.77)
2+	0.93 (0.62, 1.38)	**1.56 (1.28, 1.89)**	1.35 (0.73,2.48)
Diseases of female genital organs	**1.84 (1.55, 2.18)**	**1.53 (1.36, 1.72)**	**1.49 (1.29, 1.71)**
Inflammatory diseases of female pelvic organs	1.27 (0.75, 2.15)	**1.55 (1.15, 2.09)**	**1.48 (1.04, 2.12)**
Cervicitis and endocervicitis	1.41 (0.41, 4.91)	**2.10 (1.10, 3.99)**	**2.61 (1.18, 5.73)**
Menstrual disorders	**2.04 (1.53, 2.74)**	**1.46 (1.21, 1.76)**	**1.49 (1.17, 1.88)**
Ovarian cyst	**1.83 (1.08, 3.10)**	**1.64 (1.20, 2.24)**	**1.47 (1.02, 2.11)**
Menopausal disorders	**2.15 (1.30, 3.56)**	**1.63 (1.24, 2.12)**	**1.78 (1.37, 2.33)**
Female infertility	1.39 (0.52, 3.66)	1.60 (0.88, 2.89)	1.56 (0.69, 3.55)
Other female genital disorders	**1.69 (1.28, 2.22)**	**1.53 (1.29, 1.81)**	**1.47 (1.18, 1.84)**
Female genital pain and other symptoms	**1.63 (1.10, 2.41)**	**1.52 (1.22, 1.90)**	**1.43 (1.08, 1.88)**
Other and unspecified female genital disorders	**1.74 (1.23, 2.48)**	**1.59 (1.28, 1.99)**	**1.52 (1.13, 2.06)**
Contraceptive and procreation management, not including sterilization	**1.81 (1.21, 2.71)**	**1.53 (1.17, 1.99)**	1.19 (0.83, 1.71)
Abortion-related disorders	0.42 (0.06, 2.89)	1.56 (0.85, 2.86)	0.73 (0.22, 2.48)
Spontaneous abortion	0.46 (0.07, 3.13)	1.63 (0.87, 3.04)	0.99 (0.28, 3.42)
Induced abortion		0.59 (0.04, 9.10)	3.46 (0.09, 133.57)
Complications mainly related to pregnancy	0.93 (0.66, 1.32)	**1.63 (1.36, 1.97)**	**1.32 (1.00, 1.73)**
Ectopic pregnancy		0.73 (0.17, 3.11)	3.13 (0.19, 52.70)
Hemorrhage during pregnancy; abruptio placenta; placenta previa	0.72 (0.29, 1.82)	1.30 (0.85, 1.99)	1.60 (0.90, 2.85)
Other hemorrhage during pregnancy; childbirth and the puerperium	0.90 (0.32, 2.56)	**1.60 (1.01, 2.53)**	**2.13 (1.14, 3.98)**
Hypertension complicating pregnancy; childbirth and the puerperium	0.60 (0.19, 1.91)	0.84 (0.47, 1.50)	1.32 (0.67, 2.59)

Table 3.4 Continued

Diagnosis	0-1 years after cancer diagnosis HR (99% CI)	1-5 years after cancer diagnosis HR (99% CI)	5-10 years after cancer diagnosis HR (99% CI)
Preeclampsia and eclampsia	0.61 (0.12, 3.16)	1.02 (0.41, 2.54)	1.66 (0.71, 3.88)
Early or threatened labor	0.61 (0.28, 1.35)	1.34 (0.89, 2.01)	1.44 (0.86, 2.44)
Prolonged pregnancy	0.70 (0.14, 3.53)	1.09 (0.59, 2.01)	0.60 (0.21, 1.71)
Diabetes or abnormal glucose tolerance	0.98 (0.27, 3.58)	**2.14 (1.23, 3.73)**	1.43 (0.57, 3.57)
Other complications of pregnancy	1.18 (0.81, 1.71)	**1.93 (1.59, 2.35)**	**1.50 (1.12, 2.02)**
Missed abortion	0.81 (0.19, 3.53)	**2.16 (1.26, 3.73)**	1.20 (0.52, 2.77)
Other and unspecified complications of pregnancy	1.42 (0.96, 2.09)	**2.17 (1.76, 2.67)**	**1.64 (1.21, 2.23)**
Fetal distress and abnormal forces of labor	1.01 (0.28, 3.67)	0.62 (0.31, 1.25)	0.85 (0.26, 2.75)
Premature rupture of membranes		1.18 (0.50, 2.78)	**3.13 (1.17, 8.37)**
Complications during labor	**0.56 (0.33, 0.94)**	1.23 (0.98, 1.55)	1.19 (0.84, 1.68)
Normal delivery	0.46 (0.17, 1.19)	1.05 (0.72, 1.54)	1.04 (0.57, 1.91)

All HR adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race

Table 3.5: Reproductive and pregnancy outcomes among thyroid cancer survivors compared to the general population cohort, by cancer stage and years since cancer diagnosis

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Localized	Regional/Distant	Localized	Regional/Distant
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Total number of health conditions of female genital organs				
1	**1.30 (1.10, 1.53)**	**1.57 (1.18, 2.09)**	0.92 (0.62, 1.35)	1.79 (0.87, 3.70)
2+	**1.71 (1.37, 2.12)**	1.42 (0.97, 2.07)	1.22 (0.64, 2.32)	0.81 (0.25, 2.65)
Total number of health conditions of pregnancy, childbirth, and the puerperium				
1	0.95 (0.70, 1.29)	0.68 (0.41, 1.14)	0.96 (0.28, 3.26)	0.14 (0.01, 2.71)
2+	**1.59 (1.26, 2.01)**	**1.49 (1.0 5, 2.11)**	1.18 (0.53, 2.61)	1.55 (0.58, 4.10)
Diseases of female genital organs	**1.52 (1.33, 1.73)**	**1.57 (1.25, 1.99)**	**1.53 (1.30, 1.80)**	**1.37 (1.02, 1.84)**
Inflammatory diseases of female pelvic organs	**1.45 (1.01, 2.06)**	**1.82 (1.04, 3.18)**	1.48 (0.98, 2.22)	1.54 (0.74, 3.19)
Cervicitis and endocervicitis	1.44 (0.67, 3.12)	**8.01 (1.66, 38.71)***	**2.61 (1.10, 6.18)**	3.39 (0.32, 36.08)
Menstrual disorders	**1.52 (1.22, 1.87)**	1.30 (0.88, 1.91)	**1.57 (1.20, 2.06)**	1.24 (0.76, 2.02)
Ovarian cyst	**1.66 (1.14, 2.40)**	1.63 (0.91, 2.92)	**1.53 (1.01, 2.32)**	1.25 (0.59, 2.64)
Menopausal disorders	**1.62 (1.20, 2.18)**	1.66 (0.90, 3.07)	**1.78 (1.32, 2.39)**	1.81 (0.97, 3.39)
Female infertility	1.30 (0.63, 2.69)	2.22 (0.75, 6.53)	1.54 (0.56, 4.22)	1.70 (0.41, 7.12)
Other female genital disorders	**1.64 (1.35, 1.99)**	1.22 (0.85, 1.76)	**1.50 (1.17, 1.93)**	1.44 (0.90, 2.30)
Female genital pain and other symptoms	**1.59 (1.23, 2.05)**	1.33 (0.84, 2.11)	**1.50 (1.10, 2.05)**	1.20 (0.66, 2.20)
Other and unspecified female genital disorders	**1.72 (1.34, 2.21)**	1.20 (0.73, 1.98)	**1.45 (1.03, 2.06)**	**1.88 (1.02, 3.48)**
Contraceptive and procreation management, not including sterilization	**1.56 (1.14, 2.12)**	1.47 (0.89, 2.42)	1.24 (0.81, 1.88)	1.06 (0.51, 2.21)
Abortion-related disorders	1.78 (0.88, 3.59)	1.07 (0.31, 3.73)	0.30 (0.04, 2.24)	2.09 (0.40, 10.93)
Spontaneous abortion	1.93 (0.93, 4.01)	1.07 (0.31, 3.73)	0.46 (0.06, 3.64)	2.09 (0.40, 10.93)
Induced abortion	0.76 (0.05, 12.86)		3.46 (0.09, 133.57)	
Complications mainly related to pregnancy	**1.70 (1.37, 2.12)**	**1.48 (1.06, 2.08)**	1.24 (0.88, 1.75)	1.47 (0.93, 2.33)
Ectopic pregnancy	0.52 (0.07, 3.69)	1.47 (0.09, 23.04)	1.02 (0.01, 89.47)	
Hemorrhage during pregnancy; abruptio placenta; placenta previa	1.52 (0.92, 2.50)	0.88 (0.37, 2.08)	1.25 (0.59, 2.65)	2.39 (0.92, 6.19)
Other hemorrhage during pregnancy; childbirth and the puerperium	**1.92 (1.12, 3.28)**	1.07 (0.43, 2.68)	1.79 (0.79, 4.02)	**3.23 (1.10, 9.48)**

Table 3.5 Continued

Diagnosis	0-1 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Localized HR (99% CI)	Regional/Distant HR (99% CI)	Localized HR (99% CI)	Regional/Distant HR (99% CI)
Hypertension complicating pregnancy; childbirth and the puerperium	0.76 (0.37, 1.54)	1.05 (0.37, 2.97)	1.39 (0.60, 3.23)	1.24 (0.39, 3.90)
Preeclampsia and eclampsia	0.99 (0.33, 2.94)	1.17 (0.22, 6.40)	1.83 (0.66, 5.09)	1.38 (0.29, 6.52)
Early or threatened labor	1.33 (0.82, 2.18)	1.37 (0.65, 2.88)	1.27 (0.48, 3.34)	1.45 (0.35, 6.04)
Prolonged pregnancy	1.15 (0.55, 2.42)	0.97 (0.32, 2.94)	0.53 (0.13, 2.12)	0.65 (0.13, 3.38)
Diabetes or abnormal glucose tolerance	**1.96 (1.00, 3.84)**	2.65 (0.95, 7.35)	1.28 (0.41, 4.01)	2.30 (0.44, 11.87)
Other complications of pregnancy	**2.01 (1.59, 2.55)**	**1.77 (1.24, 2.54)**	1.44 (0.99, 2.08)	**1.67 (1.01, 2.77)**
Missed abortion	**2.26 (1.21, 4.20)**	1.87 (0.59, 5.92)	1.37 (0.52, 3.60)	0.88 (0.16, 4.77)
Other and unspecified complications of pregnancy	**2.30 (1.79, 2.96)**	**1.91 (1.32, 2.78)**	**1.58 (1.08, 2.32)**	**1.78 (1.06, 3.01)**
Fetal distress and abnormal forces of labor	0.73 (0.34, 1.56)	0.35 (0.05, 2.36)	0.62 (0.12, 3.10)	1.49 (0.24, 9.23)
Premature rupture of membranes	1.13 (0.36, 3.52)	1.43 (0.37, 5.53)	2.67 (0.90, 7.93)	7.00 (0.58, 84.36)
Complications during labor	1.24 (0.93, 1.65)	1.23 (0.84, 1.82)	1.12 (0.72, 1.74)	1.32 (0.76, 2.31)
Normal delivery	1.05 (0.66, 1.66)	1.06 (0.54, 2.11)	1.10 (0.53, 2.31)	0.93 (0.33, 2.64)

All HR adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race

*Hazard Ratios between age groups within follow-up periods are statistically significant p-value <0.05

Table 3.6: Reproductive and pregnancy outcomes among thyroid cancer survivors compared to the general population cohort, by treatment and years since cancer diagnosis

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Surgery Only HR (99% CI)	Surgery and RAI HR (99% CI)	Surgery Only HR (99% CI)	Surgery and RAI HR (99% CI)
Total number of health conditions of female genital organs				
1	**1.32 (1.07, 1.63)**	**1.42 (1.17, 1.73)**	0.96 (0.59, 1.55)	1.12 (0.68, 1.83)
2+	**1.60 (1.22, 2.10)**	**1.69 (1.30, 2.20)**	1.31 (0.57, 3.03)	0.97 (0.44, 2.11)
Total number of health conditions of pregnancy, childbirth, and the puerperium				
1	0.78 (0.51, 1.19)	0.94 (0.67, 1.31)	0.68 (0.05, 9.46)	0.60 (0.18, 1.99)
2+	**1.57 (1.16, 2.12)**	**1.49 (1.15, 1.93)**	1.12 (0.42, 2.95)	1.50 (0.64, 3.50)
Diseases of female genital organs	**1.49 (1.26, 1.77)**	**1.61 (1.37, 1.88)**	**1.45 (1.19, 1.77)**	**1.53 (1.25, 1.87)**
Inflammatory diseases of female pelvic organs	**1.63 (1.06, 2.50)**	1.50 (0.98, 2.29)	1.53 (0.90, 2.59)	1.40 (0.85, 2.31)
Cervicitis and endocervicitis	2.44 (0.96, 6.18)	1.83 (0.72, 4.66)	3.15 (0.81, 12.32)	1.89 (0.64, 5.55)
Menstrual disorders	**1.51 (1.15, 1.99)**	**1.45 (1.12, 1.87)**	**1.47 (1.04, 2.08)**	**1.56 (1.12, 2.16)**
Ovarian cyst	1.50 (0.92, 2.42)	**1.84 (1.21, 2.78)**	1.33 (0.78, 2.26)	1.51 (0.90, 2.51)
Menopausal disorders	**1.51 (1.04, 2.21)**	**1.80 (1.22, 2.64)**	**1.47 (1.00, 2.15)**	**2.18 (1.48, 3.22)**
Female infertility	1.37 (0.51, 3.67)	1.84 (0.87, 3.91)	1.89 (0.50, 7.11)	1.68 (0.56, 4.99)
Other female genital disorders	**1.54 (1.20, 1.96)**	**1.55 (1.21, 1.98)**	**1.45 (1.06, 1.98)**	**1.46 (1.07, 2.01)**
Female genital pain and other symptoms	**1.63 (1.20, 2.23)**	**1.38 (1.00, 1.92)**	1.43 (0.98, 2.08)	1.43 (0.95, 2.14)
Other and unspecified female genital disorders	**1.53 (1.10, 2.11)**	**1.72 (1.26, 2.35)**	**1.66 (1.07, 2.59)**	1.39 (0.91, 2.12)
Contraceptive and procreation management, not including sterilization	1.43 (0.94, 2.18)	**1.54 (1.09, 2.19)**	1.15 (0.66, 2.01)	1.13 (0.68, 1.86)
Abortion-related disorders	1.62 (0.69, 3.84)	1.49 (0.60, 3.71)	0.22 (0.01, 3.57)	1.71 (0.41, 7.17)
Spontaneous abortion	1.70 (0.68, 4.20)	1.55 (0.62, 3.89)	0.22 (0.01, 3.86)	2.44 (0.55, 10.78)
Induced abortion	2.33 (0.09, 58.11)			
Complications mainly related to pregnancy	**1.56 (1.17, 2.08)**	**1.63 (1.27, 2.09)**	1.20 (0.78, 1.85)	1.26 (0.86, 1.83)
Ectopic pregnancy	0.33 (0.02, 4.96)	1.30 (0.21, 7.93)		
Hemorrhage during pregnancy; abruptio placenta; placenta previa	1.34 (0.70, 2.56)	1.24 (0.69, 2.23)	1.09 (0.42, 2.83)	1.95 (0.90, 4.24)
Other hemorrhage during pregnancy; childbirth and the puerperium	1.73 (0.87, 3.44)	1.52 (0.80, 2.86)	1.37 (0.48, 3.88)	**2.71 (1.16, 6.33)**

Table 3.6 Continued

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Surgery Only HR (99% CI)	Surgery and RAI HR (99% CI)	Surgery Only HR (99% CI)	Surgery and RAI HR (99% CI)
Hypertension complicating pregnancy; childbirth and the puerperium	0.87 (0.38, 2.02)	0.81 (0.36, 1.83)	1.37 (0.48, 3.89)	1.06 (0.39, 2.86)
Preeclampsia and eclampsia	0.73 (0.18, 3.03)	1.31 (0.39, 4.41)	1.73 (0.49, 6.04)	1.30 (0.33, 5.06)
Early or threatened labor	1.17 (0.63, 2.20)	1.40 (0.80, 2.43)	1.02 (0.30, 3.54)	1.38 (0.45, 4.18)
Prolonged pregnancy	0.86 (0.27, 2.77)	0.98 (0.45, 2.13)	0.66 (0.13, 3.40)	0.40 (0.08, 1.91)
Diabetes or abnormal glucose tolerance	**2.53 (1.02, 6.31)**	1.98 (0.97, 4.06)	2.02 (0.60, 6.80)	0.74 (0.14, 3.86)
Other complications of pregnancy	**1.90 (1.40, 2.57)**	**1.90 (1.46, 2.48)**	1.39 (0.88, 2.21)	1.43 (0.95, 2.15)
Missed abortion	**3.08 (1.36, 6.99)**	1.52 (0.70, 3.28)	0.68 (0.13, 3.48)	1.58 (0.59, 4.23)
Other and unspecified complications of pregnancy	**2.17 (1.57, 3.00)**	**2.11 (1.60, 2.78)**	1.43 (0.89, 2.32)	**1.67 (1.10, 2.54)**
Fetal distress and abnormal forces of labor	0.66 (0.22, 1.98)	0.54 (0.20, 1.41)	0.32 (0.02, 5.40)	0.94 (0.22, 4.10)
Premature rupture of membranes	1.72 (0.53, 5.64)	0.81 (0.22, 2.93)	2.13 (0.54, 8.34)	**5.17 (1.16, 22.99)**
Complications during labor	1.32 (0.91, 1.90)	1.12 (0.82, 1.52)	0.88 (0.50, 1.55)	1.31 (0.83, 2.07)
Normal delivery	1.19 (0.66, 2.15)	0.90 (0.53, 1.52)	0.99 (0.37, 2.63)	1.06 (0.48, 2.33)

All HR adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race
RAI: radioactive iodine

Table 3.7: Reproductive and pregnancy outcomes among thyroid cancer survivors compared to the general population cohort, by BMI and years since cancer diagnosis

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Normal	Overweight/Obese	Normal	Overweight/Obese
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Total number of health conditions of female genital organs				
1	**1.31 (1.10, 1.56)**	**1.53 (1.21, 1.93)**	1.07 (0.88, 1.31)	1.30 (0.98, 1.73)
2+	**1.74 (1.39, 2.18)**	**1.44 (1.06, 1.97)**	1.04 (0.80, 1.17)	1.12 (0.75, 1.68)
Total number of health conditions of pregnancy, childbirth, and the puerperium				
1	0.92 (0.69, 1.23)	0.91 (0.51, 1.61)	0.95 (0.65, 1.40)	1.56 (0.82, 2.97)
2+	**1.51 (1.22, 1.87)**	**1.53 (1.01, 2.33)**	1.30 (0.94, 1.81)	0.93 (0.42, 2.06)
Diseases of female genital organs	**1.53 (1.34, 1.76)**	**1.58 (1.32, 1.91)**	**1.45 (1.24, 1.70)**	**1.38 (1.10, 1.73)**
Inflammatory diseases of female pelvic organs	**1.68 (1.17, 2.40)**	1.32 (0.81, 2.13)	1.45 (0.96, 2.20)	1.37 (0.74, 2.52)
Cervicitis and endocervicitis	**3.05 (1.38, 6.73)**	1.06 (0.40, 2.84)*	2.27 (0.92, 5.61)	2.00 (0.54, 7.46)
Menstrual disorders	**1.45 (1.15, 1.83)**	**1.35 (1.00, 1.83)**	**1.40 (1.06, 1.85)**	1.38 (0.93, 2.06)
Ovarian cyst	**1.91 (1.31, 2.78)**	1.42 (0.84, 2.39)	1.49 (0.98, 2.26)	1.24 (0.64, 2.39)
Menopausal disorders	1.39 (0.99, 1.95)	**1.71 (1.13, 2.59)**	**1.63 (1.18, 2.25)**	**1.56 (1.03, 2.37)**
Female infertility	1.40 (0.69, 2.82)	1.86 (0.64, 5.41)	1.93 (0.85, 4.38)	0.59 (0.08, 4.35)
Other female genital disorders	**1.61 (1.31, 1.97)**	**1.35 (1.01, 1.82)**	**1.39 (1.08, 1.80)**	1.39 (0.96, 2.02)
Female genital pain and other symptoms	**1.62 (1.24, 2.10)**	1.34 (0.91, 1.95)	**1.45 (1.06, 1.98)**	1.13 (0.69, 1.86)
Other and unspecified female genital disorders	**1.63 (1.25, 2.13)**	**1.50 (1.03, 2.18)**	1.35 (0.94, 1.93)	**1.77 (1.09, 2.87)**
Contraceptive and procreation management, not including sterilization	**1.56 (1.16, 2.10)**	**1.73 (1.02, 2.93)**	1.21 (0.80, 1.82)	1.25 (0.62, 2.50)
Abortion-related disorders	1.19 (0.56, 2.54)	2.31 (0.82, 6.48)	1.08 (0.32, 3.57)	0.74 (0.04, 12.91)
Spontaneous abortion	1.18 (0.54, 2.59)	2.87 (0.98, 8.37)	1.19 (0.31, 4.50)	0.93 (0.05, 17.13)
Induced abortion	0.67 (0.04, 10.95)		0.97 (0.05, 20.16)	
Complications mainly related to pregnancy	**1.58 (1.29, 1.94)**	1.43 (0.96, 2.13)	1.13 (0.83, 1.54)	1.40 (0.77, 2.56)
Ectopic pregnancy	1.21 (0.28, 5.29)		2.12 (0.22, 19.99)	5.34 (0.13, 221.91)
Hemorrhage during pregnancy; abruptio placenta; placenta previa	1.18 (0.72, 1.93)	2.06 (0.85, 5.04)	1.65 (0.86, 3.15)	1.97 (0.59, 6.64)
Other hemorrhage during pregnancy; childbirth and the puerperium	1.41 (0.83, 2.40)	2.59 (0.98, 6.87)	**2.02 (1.00, 4.07)**	3.01 (0.80, 11.26)

Table 3.7 Continued

Diagnosis	1-5 years after cancer diagnosis		5-10 years after cancer diagnosis	
	Normal HR (99% CI)	Overweight/Obese HR (99% CI)	Normal HR (99% CI)	Overweight/Obese HR (99% CI)
Hypertension complicating pregnancy; childbirth and the puerperium	0.93 (0.47, 1.82)	0.58 (0.17, 2.01)	1.08 (0.49, 2.35)	1.92 (0.53, 6.99)
Preeclampsia and eclampsia	0.70 (0.20, 2.43)	0.64 (0.09, 4.62)	1.55 (0.61, 3.91)	1.50 (0.26, 8.78)
Early or threatened labor	1.11 (0.55, 2.24)	0.78 (0.18, 3.30)	1.41 (0.59, 3.40)	0.61 (0.08, 4.56)
Prolonged pregnancy	0.83 (0.40, 1.71)	2.70 (0.84, 8.68)	0.47 (0.14, 1.61)	1.29 (0.17, 10.09)
Diabetes or abnormal glucose tolerance	**2.01 (1.04, 3.88)**	1.94 (0.73, 5.11)	1.41 (0.54, 3.68)	1.71 (0.28, 10.35)
Other complications of pregnancy	**1.90 (1.52, 2.36)**	**1.74 (1.15, 2.64)**	1.36 (0.98, 1.89)	1.41 (0.74, 2.68)
Missed abortion	1.57 (0.80, 3.08)	**3.93 (1.44, 10.72)**	1.22 (0.50, 2.99)	0.78 (0.10, 6.08)
Other and unspecified complications of pregnancy	**2.14 (1.70, 2.70)**	**1.92 (1.23, 2.98)**	**1.47 (1.04, 2.07)**	1.55 (0.79, 3.01)
Fetal distress and abnormal forces of labor	0.58 (0.26, 1.29)	0.68 (0.16, 2.81)	0.91 (0.25, 3.30)	0.58 (0.04, 9.33)
Premature rupture of membranes	1.32 (0.54, 3.23)	0.52 (0.03, 8.00)	1.36 (0.43, 4.25)	**10.31 (1.17, 90.49)***
Complications during labor	1.21 (0.95, 1.55)	1.20 (0.69, 2.10)	1.23 (0.85, 1.77)	1.12 (0.48, 2.60)
Normal delivery	1.12 (0.75, 1.66)	0.35 (0.07, 1.65)	0.97 (0.51, 1.87)	0.73 (0.14, 3.76)

All HR adjusted for baseline Charlson Comorbidity Index, race, birth state (Utah/not Utah), and age at cancer diagnosis

*Hazard Ratios between age groups within follow-up periods are statistically significant p-value <0.01

CHAPTER 4

THYROID CANCER COSTS FOLLOWING DIAGNOSIS

4.1 Abstract

Thyroid cancer affects a younger population than most adult cancers and nearly 40% of survivors declare bankruptcy within 5 years of diagnosis. With thyroid cancer being the most rapidly increasing cancer in the United States it is important to understand the costs impacting thyroid cancer patients during and after cancer treatment. The aim of this study was to determine total healthcare costs in the year of thyroid cancer treatment and the following year.

Thyroid cancer survivors diagnosed in 2013 were identified by the Utah Cancer Registry and linked to claims data in the All Payer Claims Database. Costs were calculated for the year of thyroidectomy (2013) and the following year (2014). Costs were broken down into outpatient, inpatient, professional, and pharmacy costs using claim type codes. Costs were analyzed by type of thyroidectomy (partial vs. total) and age at thyroidectomy. Generalized linear models were run for cost groups with no zero costs and two-part models were run for cost groups with zero costs, both models were adjusted on type of thyroidectomy, age, sex, location (urban/rural) and Clinical Risk Group severity level.

There were 278 thyroid cancer patients who were diagnosed and underwent a thyroidectomy in 2013. Overall costs decreased 46.6% from the year of surgery ($19,721.84) to

the following year ($10,523.88) with the largest decrease being in inpatient costs (73.8%). In the year following surgery, patients who underwent a partial thyroidectomy had significantly lower costs than those who had a total thyroidectomy. In the GLM and two-part models, baseline health was the largest predictor of costs.

Thyroid cancer patients had much higher costs than average in both years. While costs decrease in the year following surgery, they are still much higher than the average regardless of thyroidectomy type or age at thyroidectomy. With such high survival and young age at diagnosis, it is important to understand how thyroid cancer healthcare costs can be decreased to create less financial toxicity for patients.

4.2 Introduction

Thyroid cancer is the most rapidly increasing cancer in the United States, with an estimated 64,300 new cases in 2016.[1] The 5-year survival rate of thyroid cancer is 98.1%.[1] There are currently over 800,000 thyroid cancer survivors in the United States.[2] Utah has the third highest incidence rate (IR) for thyroid cancer in US, with an overall rate of 19.3 per 100,000 population per year.[3] Women have a nearly three-fold risk of thyroid cancer compared to men.[4] Thyroid cancer also affects a young population, with nearly two out of three cases being diagnosed under age 55 and the median age of thyroid cancer diagnosis in the US in 2016 being 54 for men and 49 for women.[2,5]

Total costs of thyroid cancer have been increasing over time, largely due to the increasing rates of thyroid cancer.[6] It was reported that the societal cost of thyroid cancer in 2013 for all patients diagnosed after 1985 was $1.6 billion with 37% going to surveillance of survivors[6]. Aschebrook-Kilfoy et al. estimated that by 2019 the incidence of papillary thyroid cancer would double largely due to increased surveillance and diagnostics.[7] They estimated the

total cost for those diagnosed between 2010 and 2019 to be between 18 and 21 billion dollars.[7] Cumulative costs for the first year after thyroid cancer diagnosis for patients on Medicare was $17,669 per patient and $48,989 per patient for the first 5 years.[8]

Several treatment options exist for the treatment of thyroid cancer. The primary treatment is surgery to remove all or part of the thyroid. A significant proportion of patients also receive adjuvant radioactive iodine (RAI) and thyroid stimulating hormone (TSH) suppression therapy. Haymart et al. reported that the use of RAI significantly increased between 1990 to 2008 with 56.0% of thyroid cancer patients receiving RAI in 2008.[9] Thyroid cancer patients likely also receive TSH replacement therapy.

While thyroid cancer costs are not high when comparing to other cancers, thyroid cancer patients have been reported to experience financial toxicity and have high rates of bankruptcy.[7,10-12] More than 40% of thyroid cancer patients declared bankruptcy in the first 5 years after cancer diagnosis.[10] With such high 5-year survival in thyroid cancer patients, it is important to understand the costs these patients are facing and what can be done to reduce the financial toxicity. The aim of this study was to determine the total healthcare costs in the first 2 years after thyroid cancer surgery.

4.3 Methods

The Utah All Payer Claims Database (APCD) contains healthcare claims in 2013 and 2014. Utah's APCD includes pharmacy, medical, and dental claims from private health insurance carriers, Medicaid, and third party administrators in Utah.[13] The final cohort included thyroid cancer patients identified by the Utah Cancer Registry (UCR) who had a thyroidectomy in 2013. We identified patients who had a thyroidectomy using Current Procedural Terminology (CPT) codes. Using these codes, thyroidectomies were further divided into total (CPT codes: 60210,

60240, 60525, 60254, 60260, 60271, and 60270) and partial (CPT codes: 60200, 60212, 60220, and 60225).

Utah Small Areas were reported in the APCD data. Each Small Area is made up of one or more zip codes. The average population in a Utah Small Area was approximately 46,000 in 2013 with a range from 22,300 to 120,940.[14] The zip codes were linked to the Rural Urban Commuting Area Codes (RUCA) Version 2.0 and each zip code was designated as either urban or rural based on the RUCA level.[15] Of the 63 Small Areas, 54 of them had zip codes that all fell under the same classification (e.g. all urban or all rural). Of the 9 that had both classifications, all had a majority for either rural or urban. The majority was used to classify the Small Area. Clinical Risk Groups (CRGs) were also reported in the data. This is a classification system created by 3M™ Health Information Systems to classify people into clinically meaningful severity levels based on inpatient and ambulatory diagnosis and procedure codes, pharmacy data, and functional health status.[16] The severity levels ranged from 0-6 with 0 being the lowest severity.

Costs were calculated for the calendar year of 2013 starting when the thyroidectomy occurred. Costs were also calculated for the calendar year of 2014. Costs were adjusted to 2014 dollars to reflect inflation using the Medical Care Consumer Price Index (CPI).[17] Costs for each claim were the sum of copayment, coinsurance, deductible, and reimbursement. Out of pocket expanses were also calculated as the sum of copayment, coinsurance, and deductible. All costs were divided into facility (outpatient and inpatient), and professional using claim type codes. Pharmacy costs were also calculated. Total cost of care for each year and costs from the time of surgery to end of 2014 were also reported. Costs were reported overall as well as stratified by type of thyroidectomy and age of diagnosis. Healthcare utilization was determined by the number of visits per patient, which was broken down into the same categories as costs.

As the data were not normally distributed, Mann-Whitney tests were used to compare

the costs by type of thyroidectomy and Kruskal-Wallis tests were used to compare costs and healthcare utilization by age of diagnosis since there were three age categories (<40, 40-64, ≥65). For cost categories with no zero costs, generalized linear models were model run with a gamma distribution and log link to account for the non-normal distribution of costs. There were four categories with no zeros: professional costs in 2013, overall and total costs in 2013, and overall costs. If the cost category had any zero costs, two-part models were run. The first model for the zero costs was a probit model and the second model was the same GLM model used for the categories with no zero costs.[18] All models were adjusted for type of thyroidectomy, age, sex, location (urban/rural), and CRG severity level. All the coefficients in the regressions were reported in costs. A subset analysis was also run on those diagnosed with thyroid cancer before age 65 to determine if the predictors of costs were the same. All analyses were completed in SAS (version 9.4) and Stata 14.

4.4 Results

The final study population included 278 thyroid cancer patients who underwent a thyroidectomy in 2013. The majority underwent a total thyroidectomy (77.3%), were female (76.6%), and lived in urban areas (83.1%) as shown in Table 4.1. The total average costs in 2013 starting at the time of the thyroidectomy were $19,721.84 (Table 4.2). In 2014, the average cost reduced to $10,523.88. The biggest drop between the 2 years was with inpatient costs dropping from an average of 10,218.05 in 2013 to $3,510.21 in 2014. Pharmacy costs rose 112% between 2013 and 2014. The average number of visits dropped from 40.0 in 2013 to 25.3 in 2014, a 36% decrease. Inpatient visits decreased by the highest percentage compared to other costs between 2013 and 2014, with a 73.8% decrease. Figure 4.1 shows the out of pocket costs for thyroid cancer patients in both years. On average thyroid cancer patients paid $2,244.47 out of

pocket in 2013 and $1,528.43 in 2014.

Figures 4.2 and 4.3 show the costs in 2013 and 2014 stratified by type of thyroidectomy and age at thyroidectomy, respectively. Costs were also run stratified by gender with no significant differences in any costs in 2013 or 2014. There were also no significant differences in type of thyroidectomy or age by gender. In 2013, patients who underwent a partial thyroidectomy had higher total healthcare costs than those who underwent a total thyroidectomy ($21,137.32 vs. $19,307.07). There was a significant difference between these two groups for outpatient costs in 2013 with those who had a partial thyroidectomy having an average of $4,024.59 compared to $2,311.50 for those who had a total thyroidectomy (p-value=0.0117). However, in 2014 patients who had a total thyroidectomy had significantly higher average total costs ($11,624.59 vs. $6,767.50, p-value=0.0381). The average number of visits was similar between the groups in 2013, with patients who had a total thyroidectomy having an average of 39.9 visits compared to 40.1 for patients who had a partial thyroidectomy (Table 4.3). While there were no significant differences between the number of visits in 2014, patients who had a partial thyroidectomy showed a greater reduction from 2013 (46.9% vs. 33.8%).

Thyroid cancer patients who had a thyroidectomy after age 65 had the lowest average total cost in 2013 with an average of $14,711.04 compared to $19,464.15 for those under age 40 and $20,964.04 for between 40 and 64 years old. All costs except pharmacy costs were the lowest for people age 65 and older. Average pharmacy costs were significantly lower for patients who underwent a thyroidectomy at younger ages ($371.01 for <40, $1,110.12 for 40-64, and $1,589.54 for 65+, p-value=0.0022). Average total costs decreased for all ages between 2013 and 2014 but decreased the least for those 65 and older (-62.0% for <40, -42.6% for 40-64, and -7.7% for 65+). The youngest group of patients had the lowest costs in 2014

($7,402.67).There was a significant increase in visits in both 2013 and 2014 as the age at thyroidectomy increased. In 2013, those who had a thyroidectomy before the age of 40 had an average of 31.4 visits, while those 65 and older at time of thyroidectomy had an average of 50.9 visits (Table 4.4). However, all three age groups had a similar percentage decrease in number of visits between 2013 and 2014. In 2013, there was a statistically significant difference in number of professional visits (p-value=0.0086), pharmacy visits (p-value=0.0009), and total visits (p-value=0.0007). Only the professional visits (p-value=0.0184) and total visits (p-value=0.0366) remained significantly different across all three age groups in 2014.

Overall the GLM and two-part models showed that baseline health was the most commonly significant predictor of costs (Table 4.5). Age was a significant predictor for costs during the year of the thyroidectomy, but not for any costs during 2014. In 2013, the total cost was an estimated $7,667.59 higher for people under the age of 65 (p-value=0.010). The type of thyroidectomy was only a significant cost predictor for outpatient costs in 2013 with those who received a total thyroidectomy having an estimated $1,630.99 lower costs than those who received a partial thyroidectomy (p-value=0.010). A 1 level increase in the Clinical Risk Group severity level led to an estimated increase of $2,169.59 in 2013 (p-value=0.011) and $3,624.69 in 2014 (p-value=0.005). Thyroid cancer patients living in urban areas had an estimated $3,449.73 higher in 2013 professional costs than those in rural areas (p-value=0.003). Living in an urban vs. rural area was not a significant predictor for any other costs in 2013 or 2014. There were very few differences in the subgroup analysis of those diagnosed before age 65. The same predictors which were significant in the full model were significant in the subgroup analyses.

4.5 Discussion

In this population of thyroid cancer patients who underwent a thyroidectomy in 2013, the overall costs were significantly higher in the year of the thyroidectomy. This is expected as the largest change came from inpatient costs, where the thyroidectomy likely occurred. Also, as expected, pharmacy costs increased in 2014, the year after thyroid cancer occurred. As most of these patients are likely on either hormone replacement or hormone suppression therapy after surgery, the pharmacy costs would be expected to rise following surgery. The overall costs for thyroid cancer patients in both 2013 and 2014 were higher than the average healthcare costs per person in Utah, which were $3,188 on average in 2014 as reported by the Utah APCD. For another comparison, it is estimated that people with diabetes in Utah have an estimated cost 2.3 times higher than those who don't have diabetes, which would have been approximately $7,330 in 2014.[19] Out of pocket costs were much higher than the national average, which was estimated to be $703 in 2011 ($765 in 2014 dollars).[20] These out of pocket costs can create a large burden on a cancer patient.

Outpatient costs in 2013 were significantly higher for those who received a partial thyroidectomy, which is unsurprising because partial thyroidectomies are more likely to occur in an outpatient setting, whereas a total thyroidectomy is more likely to occur in an inpatient setting. However, the costs were significantly lower in 2014 for those who underwent a partial thyroidectomy, nearly $5,000 lower. There was no significant difference in subgroup costs between these two groups in 2014, but those who received a partial thyroidectomy had lower costs in all areas of healthcare studied in the calendar year after the thyroidectomy. However, while the costs were significantly lower there were no significant differences in the healthcare utilization of these two groups. Regardless of the type of surgery patients underwent, they appeared to have similar follow-up healthcare following the surgery with patients who had a

partial thyroidectomy having slightly lower healthcare utilization. There were no significant demographic differences (age, CRG level, etc.) between the two populations to account for the differences in costs.

There are several reasons that costs could be higher for patients who received a total thyroidectomy. Patients who received a total thyroidectomy may also receive RAI postsurgery, which would not occur with patients who received a partial thyroidectomy. Also, following a total thyroidectomy, patients must be placed on TSH replacement therapy. Patients who underwent a partial thyroidectomy may not be placed on TSH hormone therapy, which would likely lead to increased spending for total thyroidectomy patients. Patients on TSH suppression therapy also receive more TSH blood tests to monitor TSH levels. Both groups of patients would receive ultrasound monitoring, which may account for a nonsignificant difference in healthcare utilization. All follow-up, whether blood tests and/or ultrasound could occur in the same visit.

As expected, those 65 and older had lower healthcare costs than younger ages due to Medicare reimbursement. This effect was shown in the stratified analysis by age as well as the two-part and GLM models. However in the models in 2014, age was no longer a significant predictor for costs. The regression with only those people diagnosed before age 65 showed the same predictors as the full model. As thyroid cancer is a young cancer, the majority of the population was diagnosed before age 65. The increased costs in those 65 and older for pharmaceutical costs can be attributed to Medicare not being able to negotiate drug prices as part of the Medicare Modernization Act of 2003. Medicare can negotiate prices of other healthcare costs with hospitals and physicians.

Baseline health was the biggest predictor of costs in the two-part and GLM models. The more severe the CRG level was, the higher the healthcare costs were. Unhealthier patients are more likely to have increased healthcare utilization and therefore higher costs.

There are several limitations to this analysis. Due to the nature of the data, we were not able to have exact dates of thyroid cancer diagnosis or thyroidectomy. Therefore, we do not know when in 2013 the patients were diagnosed or had surgery. We also were not able to obtain data for the cancer characteristics such as stage and histology as well as other treatment such as radioactive iodine, which would likely have influenced the health of the patient and healthcare costs. Insurance type was also not available in the data, which does affect how much is paid and healthcare utilization. Despite these missing data, we were able to examine costs by other factors that influence healthcare costs including age and baseline health status. Another limitation is that thyroidectomies and RAI were identified through CPT codes. It is not expected these would be incorrect as the population was identified by the Utah Cancer Registry as thyroid cancer patients. However coding errors do occur. There may have been patients who did have a thyroidectomy in 2013 and were not captured in our study population due to missing claims data. Finally, this is a narrow population of thyroid cancer patients in Utah who had a thyroidectomy in 2013. However, this allowed for the study of a homogenous population where type of thyroidectomy, age, and other factors could be studied for costs.

There are also several strengths to this study. There have been few studies on the healthcare costs of thyroid cancer patients. Many of these studies have only been able to focus on the Medicare population. We were able to examine patients of all ages and examine how costs varied by age. We were also able to examine costs by type of thyroidectomy. The data from our study included all healthcare claims reported to the All Payer Claims Database in Utah. By law, this should have included all healthcare claims that occurred in 2013 and 2014 at any healthcare payer with an enrollment of 2,500 or more covered lives, which represents around 80% of Utah's population.[21]

Overall, this study provides good insight into the healthcare utilization and costs of

thyroid cancer patients after they undergo a thyroidectomy. Baseline health of the thyroid cancer patient at the time of surgery was the largest predictor of healthcare costs, and patients who undergo a partial thyroidectomy had significantly lower costs in the calendar year following surgery than those who have a total thyroidectomy. Future studies need to examine the role other thyroid cancer treatments and insurance type have on healthcare costs and utilization as well as what can be done to improve the health of thyroid cancer patients in hopes of reducing costs as well as creating a better quality of life and reducing financial toxicity for thyroid cancer survivors.

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Table 4.1: Characteristics of thyroid cancer patients diagnosed in 2013

Variable	Frequency (%)
Sex	
Female	213 (76.6)
Male	65 (23.4)
Age	
< 40	101 (36.3)
40-65	146 (52.5)
65+	31 (11.2)
Clinical Risk Group severity level	
0	12 (4.3)
1	126 (45.3)
2	71 (25.5)
3-4	61 (21.9)
5-6	8 (2.9)
Location	
Urban	231 (83.1)
Rural	18 (6.5)
Missing	29 (10.4)
Thyroidectomy	
Total	215 (77.3)
Partial	63 (22.7)

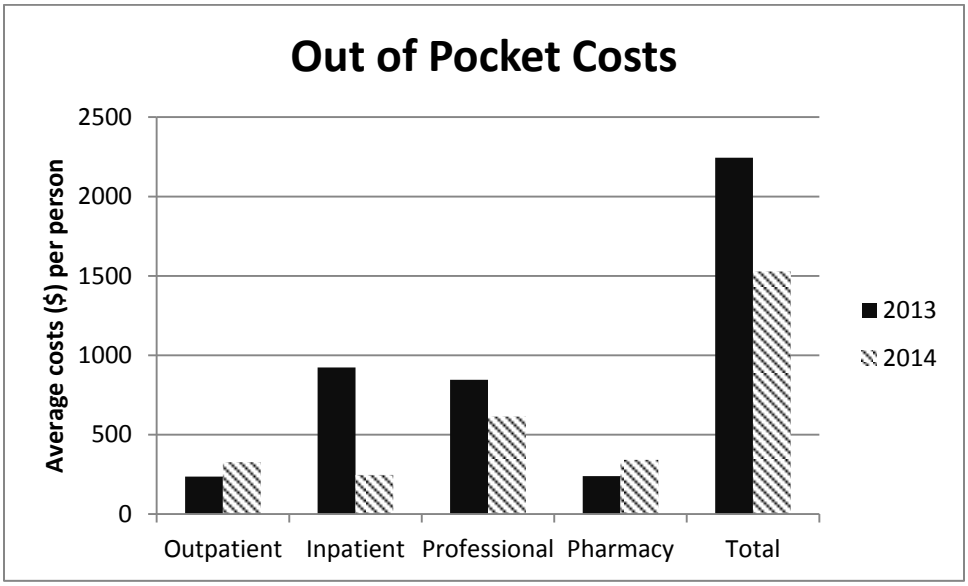

Figure 4.1: Out of Pocket Costs

Table 4.2: Overall costs and number of visits by year for thyroid cancer patients

	Average cost ($) per person (standard deviation)			Average number of visits per person (standard deviation)		
	2013	**2014**	**Overall**	**2013**	**2014**	**Overall**
Outpatient	2,699.72 (3,913.84)	2,093.02 (6,264.05)	4,792.74 (7,832.24)	4.7 (4.1)	2.0 (2.9)	6.7 (5.9)
Inpatient	10,218.05 (11,440.95)	3,510.21 (16,988.41)	13,728 (26,565.68)	1.5 (1.3)	0.4 (1.2)	1.8 (1.9)
Professional	5,909.01 (5,580.96)	3,023.95 (4,790.18)	8,932.96 (8,834.89)	18.3 (15.4)	10.1 (12.2)	28.3 (23.1)
Pharmacy	895.06 (2,021.48)	1,896.69 (6,298.01)	2,791.75 (7,282.22)	15.5 (18.0)	12.8 (18.1)	28.3 (34.1)
Total	19,721.84 (16,406.92)	10,523.88 (26,565.68)	30,245.71 (33,804.39)	40.0 (30.0)	25.3 (29.8)	65.2 (54.1)

*2013 costs and visits started at time of thyroidectomy

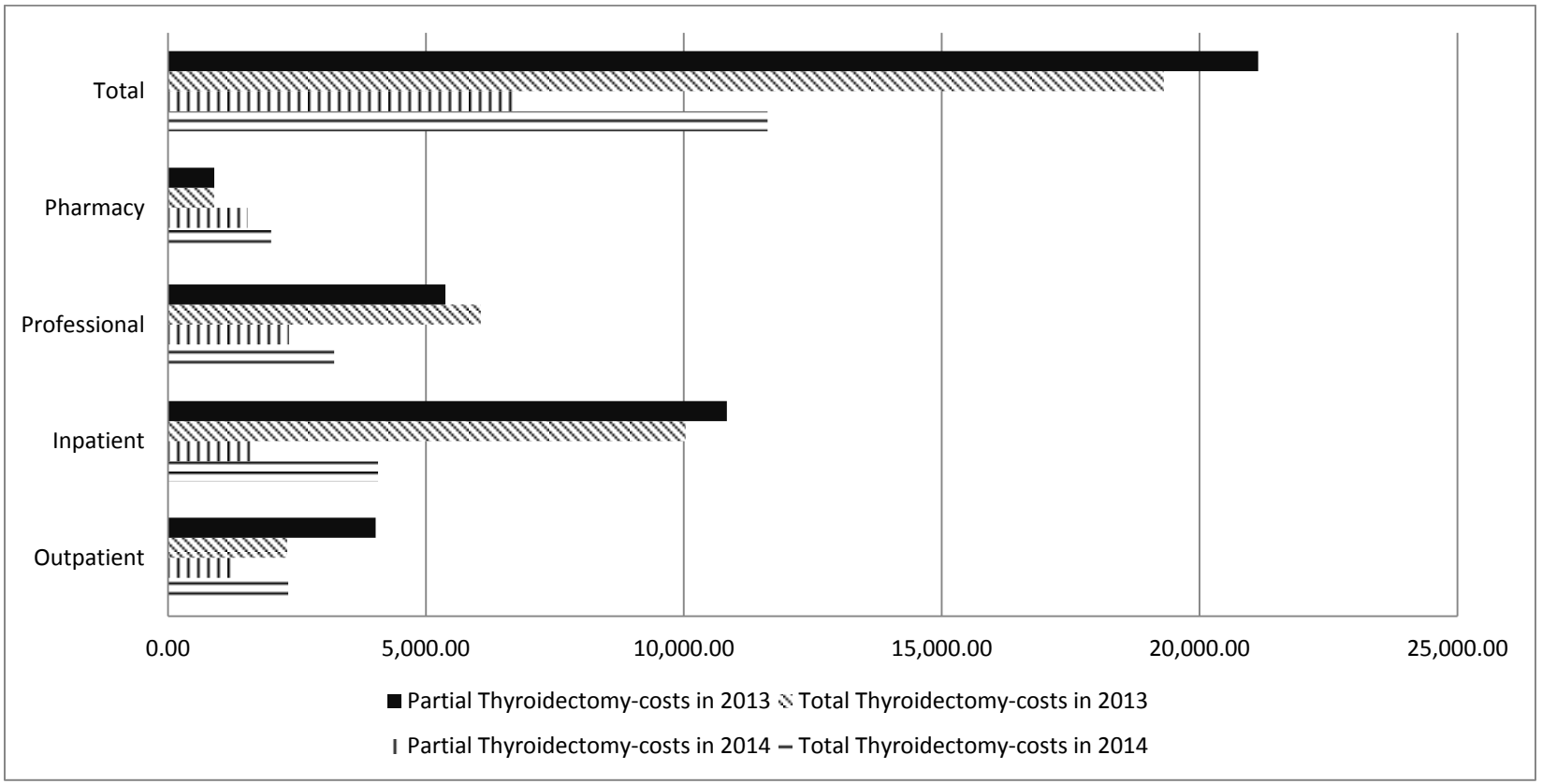

Figure 4.2: Costs by year and type of thyroidectomy

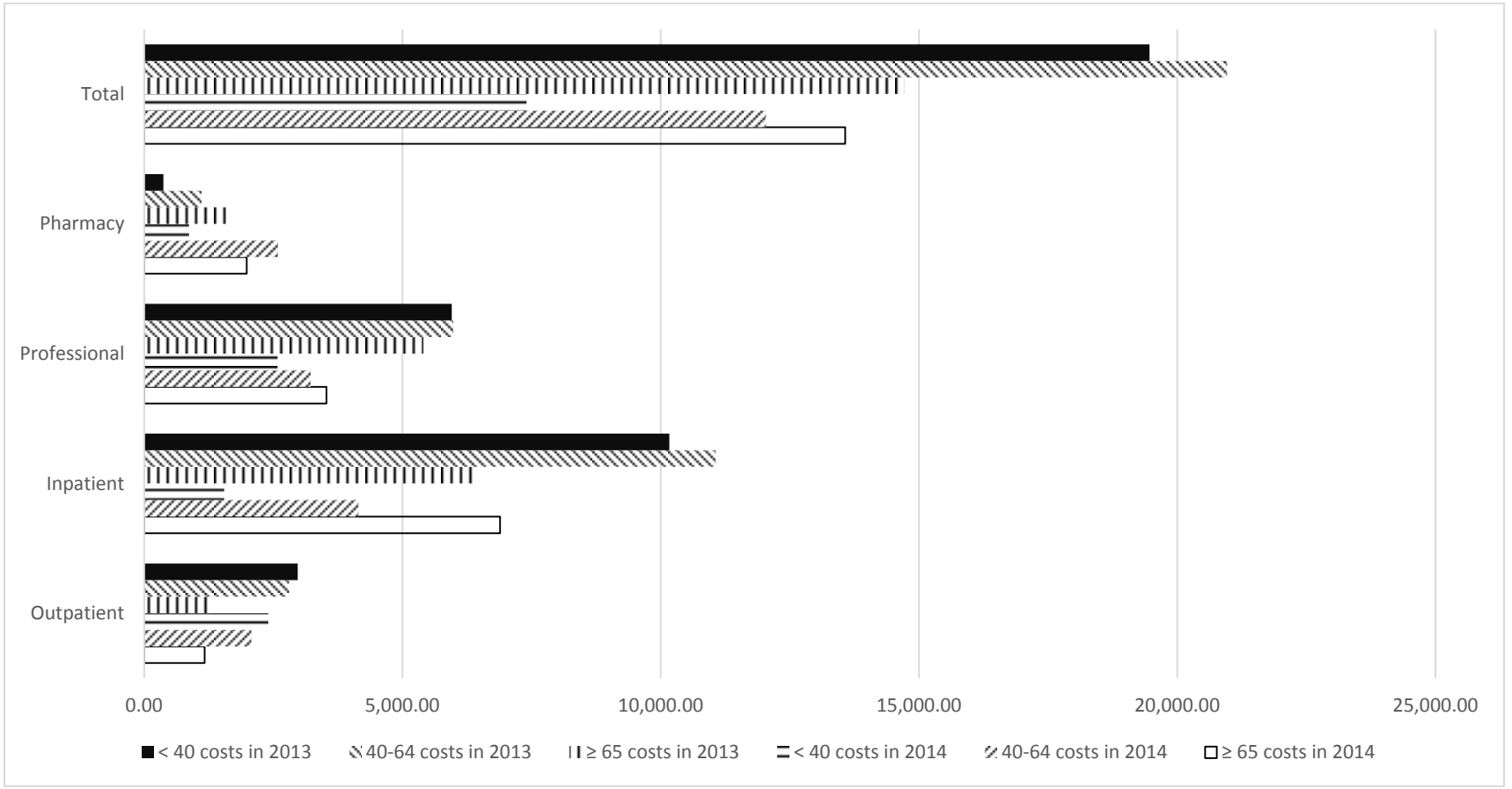

Figure 4.3: Costs by year and age at thyroidectomy

Table 4.3: Number of visits by year and type of thyroidectomy

	Number of Visits (mean(std)) 2013			Number of Visits (mean(std)) 2014		
	Total	**Partial**	**p-value**	**Total**	**Partial**	**p-value**
Outpatient	4.6 (4.1)	5.1 (4.2)	0.5488	2.1 (3.0)	1.8 (2.6)	0.3676
Inpatient	1.5 (1.3)	1.5 (1.1)	0.5998	0.4 (1.3)	0.2 (0.6)	0.3892
Professional	18.6 (16.1)	17.1 (12.4)	0.5717	10.7 (12.6)	8.0 (10.7)	0.0585
Pharmacy	15.2 (18.6)	16.4 (15.7)	0.1774	13.2 (19.0)	11.4 (14.9)	0.5514
Total	39.9 (30.6)	40.1 (28.3)	0.8712	26.4 (30.9)	21.3 (25.2)	0.1746

Table 4.4: Number of visits by year and age at thyroidectomy

	Number of Visits (mean(std)) 2013				Number of Visits (mean(std)) 2014			
	< 40	**40-64**	**65+**	**p-value**	**< 40**	**40-64**	**65+**	**p-value**
Outpatient	4.3 (3.7)	5.0 (4.3)	4.8 (4.7)	0.7090	1.7 (2.3)	2.1 (3.1)	2.5 (3.6)	0.9017
Inpatient	1.4 (1.1)	1.5 (1.4)	1.4 (1.1)	0.8015	0.2 (0.6)	0.4 (1.4)	0.6 (1.6)	0.4331
Professional	**15.4 (12.4)**	**18.9 (12.7)**	**24.8 (28.4)**	**0.0084**	8.0(9.5)	10.5 (12.3)	14.8 (17.5)	0.1794
Pharmacy	**10.3 (10.7)**	**18.2 (20.3)**	**19.9 (21.8)**	**0.0009**	9.5 (10.5)	14.8 (20.8)	14.1 (22.5)	0.8733
Total	**31.4 (21.4)**	**43.5 (31.2)**	**50.9 (40.8)**	**0.0007**	19.4 (17.0)	27.8 (33.0)	32.1 (41.9)	0.5615

Table 4.5: Treatment, patient characteristics and healthcare costs for thyroid cancer patients

	Outpatient		Inpatient		Professional		Pharmacy		Total	
	Coefficient ($)	p-value	Coefficient ($)	p-value	Coefficient ($)	p-value	Coefficient ($)	p-value	Coefficient ($)	p-value
2013 Costs										
Thyroidectomy Total vs. Partial	**-1,630.99**	**0.010**	316.93	0.858	820.62	0.242	62.75	0.866	-664.22	0.782
Sex Male vs. Female	-62.49	0.916	924.89	0.591	764.80	0.268	420.59	0.317	1,637.51	0.485
Age ≥ 65 vs. < 65	**-2,835.88**	**0.001**	**-5,351.03**	**0.025**	-1,079.41	0.245	645.20	0.270	**-7,667.59**	**0.017**
Location Urban vs. Rural	577.56	0.550	2,485.31	0.384	**3,449.73**	**0.003**	-262.45	0.653	5,662.12	0.143
Clinical Risk Group	256.76	0.239	370.62	0.534	**1,068.23**	**<0.001**	**667.53**	**0.019**	**2,169.59**	**0.011**
Constant	**2,677.64**	**<0.001**	**9,851.35**	**<0.001**	**5,851.08**	**<0.001**	**1,094.04**	**<0.001**	**19,283.06**	**<0.001**
2014 Costs										
Thyroidectomy Total vs. Partial	1,460.61	0.173	3,104.35	0.167	664.80	0.232	546.00	0.647	5,336.26	0.076
Sex Male vs. Female	441.94	0.653	-844.58	0.659	172.60	0.748	1,004.71	0.438	1,084.68	0.704
Age ≥ 65 vs. < 65	-1,405.73	0.296	2,323.79	0.248	261.80	0.714	536.73	0.727	2,112.49	0.577
Location Urban vs. Rural	-123.43	0.937	915.70	0.698	1,174.58	0.191	809.62	0.661	2,949.46	0.525

Table 4.5 Continued

	Outpatient		Inpatient		Professional		Pharmacy		Total	
	Coefficient ($)	**p-value**	**Coefficient ($)**	**p-value**	**Coefficient ($)**	**p-value**	**Coefficient ($)**	**p-value**	**Coefficient ($)**	**p-value**
Total Costs										
Clinical Risk Group	380.36	0.268	1,317.04	0.097	**853.07**	**<0.001**	960.97	0.125	**3,624.69**	**0.005**
Constant	**2,128.19**	**<0.001**	**2,905.58**	**<0.001**	**2,931.62**	**<0.001**	**2,073.08**	**0.001**	**10,065.01**	**<0.001**
Thyroidectomy										
Total vs. Partial	-802.45	0.502	2,167.73	0.412	1,484.91	0.135	592.7	0.663	3,556.36	0.386
Sex										
Male vs. Female	268.27	0.821	45.42	0.986	897.34	0.355	1,335.49	0.365	2,253.18	0.573
Age										
≥ 65 vs. < 65	**-4,290.70**	**0.014**	-158.61	0.963	-764.57	0.556	1,168.53	0.534	-4,253.33	0.431
Location										
Urban vs. Rural	879.93	0.657	3,210.98	0.443	**4,633.84**	**0.004**	504.32	0.803	8,604.82	0.191
Clinical Risk Group	614.59	0.159	**1,800.86**	**0.062**	**1,934.12**	**<0.001**	**1,703.96**	**0.048**	**5,767.86**	**<0.001**
Constant	**4,794.61**	**<0.001**	**12,743.12**	**<0.001**	**8,788.00**	**<0.001**	**3,199.76**	**<0.001**	**29,249.13**	**<0.001**

CHAPTER 5

CONCLUSION

This study had three main objectives: 1) to examine the risks of aging related diseases and health conditions separately for thyroid cancer survivors who were diagnosed before age 40 and thyroid cancer survivors who were diagnosed age 40 or later, 2) to examine the risks of reproductive and pregnancy complications following thyroid cancer for female thyroid cancer survivors diagnosed before the age of 50, and 3) to examine the healthcare costs of thyroid cancer survivors in the year of their diagnosis and the year following. The main goals were to understand the long-term health effects of thyroid cancer for survivors and to understand the cumulative costs in the year of thyroid cancer diagnosis and the following year.

5.1 Key Findings

Overall thyroid cancer survivors of all ages had increased risks for aging related diseases and health conditions when compared to a matched general population cohort. For many of the aging related outcomes studied, young thyroid cancer survivors had higher risks than older thyroid cancer survivors. While the frequency of these outcomes occurring was lower in the younger survivors, the risk was higher. With the frequencies being higher in the older cohort, both survivors and the matched general population cohort, we did not observe large effect sizes as we did in the younger cohort. It may be possible to conclude that younger thyroid cancer

survivors have accelerated rates of aging. However, the results of the risk analysis show that the treatment is not the driving force for the risks of long-term health related to aging in either age population of thyroid cancer survivors. The biggest predictors for long-term health are age at diagnosis and baseline health in both populations and year of diagnosis in those diagnosed before age 40.

Many reproductive and pregnancy complications have been previously reported to be associated with thyroid cancer treatment and radioactive iodine in particular.[5,13] We observed many of the same associations with a few differences. Menstrual disorders were to be associated with RAI in the past, but were transient with a return to normal after 1 or 2 years.[14] We observed significant increases in menstrual disorders up to 10 years after cancer diagnosis. Female thyroid cancer survivors of childbearing age were also more likely to have multiple health conditions associated with pregnancy and multiple health conditions associated with female genital organs. Many of the previous studies have reported that the majority of reproductive complications were associated with the use of RAI. However, we observed significant increased risks for these same complications and diseases in both women who only had surgery and women who had surgery and RAI. Women of childbearing age who survive thyroid cancer need to be aware of the increased risks for these reproductive and pregnancy complications.

Thyroid cancer patients and survivors have highly increased healthcare costs in the year of their diagnosis and the following year, with the average Utah healthcare costs being $3,188.[15] As expected there is a significant decrease in total costs from the year of the surgery to the following year. All subgroup costs except outpatient and pharmacy costs had a significant decrease in costs between the 2 years. Pharmacy costs had a significant increase in costs between the 2 years. While costs decrease in the year following surgery, they are still much

higher than the average regardless of thyroidectomy type or age at thyroidectomy. As thyroid cancer survivors have been shown to have high rates of bankruptcy, it is important to understand what can be done to reduce healthcare costs not just during cancer treatment but also in follow-up care in the years after cancer.[11]

Thyroid cancer affects a young population and has high survival, leading to thyroid cancer survivors often living long lives after cancer diagnosis and treatment. This study observed that thyroid cancer may be associated with increased rates of aging as survivors of all ages were observed to have increased risks for many diseases and health conditions associated with aging. Much of the risk was explained by baseline health and age at diagnosis, which may lead health care providers to be more proactive in lifestyle changes for older and less healthy thyroid cancer patients. Female thyroid cancer survivors of child-bearing age were also reported to have increased risks for reproductive and pregnancy complications. There are currently recommendations to avoid pregnancy in the year after receiving RAI; however many of the complications we observed were also observed in survivors who only underwent a thyroidectomy. We also observed an increased risk in gestational diabetes 1-5 years after cancer diagnosis, which may lead to earlier testing in pregnant women who have survived thyroid cancer.

Overall, thyroid cancer survivors are an important population to study as they often live for decades after treatment. With high rates of bankruptcy, increased healthcare costs, and increased risks for long-term health effects we need to understand what can be done to help improve thyroid cancer survivors' health which would likely also help to reduce their long-term healthcare costs.

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