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Journal
Cancer Epidemiology Biomarkers & Prevention, 26(12)

ISSN
1055-9965

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Publication Date
2017-12-01

DOI
10.1158/1055-9965.epi-17-0623

Peer reviewed

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2017 December ; 26(12): 1695–1704. doi: 10.1158/1055-9965.EPI-17-0623.

Aging-related disease risks among young thyroid cancer survivors

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Abstract

Background—Thyroid cancer is the most rapidly increasing cancer in the U.S., affects a young population, has high survival, and is one of the most common cancers in people under age 40. The aim of this study was to examine the risks of aging-related diseases in a statewide sample of thyroid cancer survivors who were diagnosed <40 years compared to those diagnosed ≥40 and a cancer-free sample.

Methods—Thyroid cancer survivors diagnosed 1997-2012 were matched to up to 5 cancer-free individuals on birth year, sex, birth state, using the statewide 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, and Charlson Comorbidity Index.

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Results—There were 3,706 thyroid cancer survivors and 15,587 matched cancer-free individuals (1,365 cases diagnosed <40 years old). Both age groups had increased risks for multiple circulatory health conditions 1-5 years after cancer diagnosis compared to cancer-free individuals. Survivors <40 had a higher risk of hypertension, cardiomyopathy, and nutritional deficiencies.

Conclusions—Increased risks for diseases associated with aging were observed for both age groups, with younger thyroid cancer survivors having higher risks for select diseases.

Impact—As thyroid cancer survivors in this study were found to have increased risks for aging-related diseases, future studies are needed to assess what can be done to reduce the increased risks of these long-term health effects.

Keywords

survivorship; thyroid cancer; aging; long-term health

Introduction

Thyroid cancer is the most rapidly increasing cancer in the United States with an estimated 64,300 new cases diagnosed in 2016 and more than 800,000 thyroid cancer survivors currently live in the U.S. [1, 2]. The 5-year relative survival rate of thyroid cancer is 98.1% [3]. In the United States, thyroid cancer affects women more than men [4]. Thyroid cancer tends to present at an earlier age than other cancers, with the median age of thyroid cancer diagnosis in the US in 2014 was 54 for men and 49 for women [5, 6]. Little is known about whether thyroid cancer survivors experience aging-related conditions, such as myocardial infarction, arthritis, osteoporosis, glaucoma, and hypertension, at a higher rate than individuals without cancer, as many of these conditions have been reported as late effects of cancer treatment [7, 8]. As cancer treatment has been associated with accelerated aging, understanding the health risks for thyroid cancer survivors is extremely important to manage their health conditions as they age [9].

Thyroid cancer is one of the most common cancers in adolescent and young adults [10]. Increasing age of thyroid cancer diagnosis has been associated with increased mortality, both overall and cancer specific, starting with diagnosis at age 40 [11]. Young thyroid cancer patients have increased overall survival and cancer specific survival compared to older patients, but may receive more aggressive treatment. The primary treatment for thyroid cancer is thyroidectomy 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. It is rare for thyroid cancer patients to be treated with chemotherapy except in the case of advanced metastatic disease. More recent guidelines have called for less treatment, which will hopefully reduce the long-term health effects that have been found in thyroid cancer survivors [12]. There has been a significant increase in the use of RAI over time [13]. However, it is unclear yet if the most recent guidelines will affect this trend or how long it will take to change the trend.

The younger thyroid cancer population is living many decades after treatment and may have increased risks for long-term health effects due to more aggressive treatment. Younger

patients (<45 years old at diagnosis) are more likely to undergo a total thyroidectomy and to receive RAI [14]. RAI has been associated with increased risks for gastrointestinal symptoms, pulmonary fibrosis, and salivary gland conditions [15-17]. TSH suppressive therapy can lead to bone mineral density loss as well as cardiac outcomes such as increased heart rate and decreased stroke volume [18-20]. Other commonly reported conditions among thyroid cancer survivors include migraine headaches, arthritis, cataracts, and hearing loss [21, 22].

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 [20-22]. 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 the risk of aging-related diseases and health conditions for thyroid cancer survivors who were diagnosed before age 40 and those who were diagnosed at age 40 or later. We use a statewide sample of thyroid cancer survivors and matched cancer-free individuals who were linked to medical records, cancer registry data, and demographic data from the Utah Department of Health to examine these risks.

Materials and Methods

This cohort was established within the Utah Population Database (UPDB), which links data from the Utah Cancer Registry (UCR) (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 [23]. The healthcare data from UPDB includes ambulatory surgery and inpatient discharge data from the entire state of Utah (1996-2012) as well as linkage to EMR data from two of the biggest healthcare providers in Utah, the University of Utah Healthcare (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 University of Utah Healthcare and/or Intermountain Healthcare EMR data. This study was approved by the University of Utah Institutional Review Board.

Primary thyroid cancer cases were identified through UCR between 1997-2012. A general population cohort of up to five cancer-free individuals were matched to each thyroid cancer patient 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 UCR 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 one year of follow-up time from cancer

diagnosis including dying within one year (n=243), or an eligible cancer-free individual could not be matched to them (n=217).

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 [24]. 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 (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.

Statistical Methods

Chi-squared tests were used to assess differences in the demographic characteristics between thyroid cancer survivors and the general population cohort, as well as within the thyroid cancer survivors by age of diagnosis. For analyses of disease risks, the aging related diagnosis was categorized over time: one to five years, greater than five to ten years, and more than ten 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 adjusted for matched variables, race, Charlson Comorbidity Index (CCI) at baseline, and baseline body mass index (BMI). The Charlson Comorbidity Index was calculated using all medical record data prior to the date of cancer diagnosis. Hazard ratios between age groups within follow-up periods were tested for statistically significant differences with an alpha of 0.01. Proportional hazards assumptions were tested for all Cox proportional hazards models. If the proportional hazard assumption was not met, a flexible cubic spline model was used. Cumulative incidence curves were calculated for selected outcomes.

The closest BMI measurement prior to cancer diagnosis and at least one year before cancer diagnosis was calculated to assess baseline BMI. We limited the BMI measurements to at least one before cancer diagnosis to try to ensure that the baseline BMI measurement was not affected by the cancer. The median time from cancer diagnosis was 3.7 years with 67% having a BMI measurement within 5 years prior to cancer diagnosis. Approximately 20% of all participants were missing BMI, thus we imputed BMI for the 20% who were missing it using cancer status, age at diagnosis, sex, race, and CCI as predictors using multiple

imputation. We compared Cox regression models including only those who had BMI in the data and with the full study population, including those who had imputed BMI, to assure that our inferences did not change due to the imputed BMI.

Since the CCS Level 3 and 4 conditions were specific, they were analyzed as incident cases only; if a participant had been diagnosed with one of the conditions before the time frame for that analyses, they were excluded from that analysis as a prevalent case. 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 (musculoskeletal, nervous, and endocrine systems), risk factor analyses were run for the 1-5 year time frame for the thyroid cancer survivors. The risk factor assessment included treatment (surgery only and surgery with RAI), hormone therapy, cancer stage, age at diagnosis, diagnosis year, sex, BMI at baseline, CCI at baseline, and number of cancers. All cases included were primary thyroid cancer cases with no previous cancers, however some had other cancers after the thyroid cancer diagnosis. We included this is as a risk factor to account for other types of treatments that may have been used for those cancers. Based on the risk factor analyses, attributable fractions were calculated. All analyses were conducted using SAS (version 9.4).

Results

The final cohort included 3,706 thyroid cancer survivors and 15,587 cancer-free individuals (Table 1). The thyroid cancer patients had significantly higher mortality (p-value < 0.0001) and higher BMI (p-value < 0.0001). Male thyroid cancer survivors were significantly more likely to be obese than female thyroid cancer survivors. This pattern also held true in the general population cohort, with males having significantly higher BMI. 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. Compared to thyroid cancer 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) and be diagnosed before 2000 (12.3% vs 8.9%, p-value <0.0001) (Supplemental Table S1). 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. The proportion of thyroid cancer survivors diagnosed with each of the diseases investigated by age group and follow-up time are shown in Supplemental Table S2. Figure 1 shows incidence curves for hypertension, heart disease, and nutritional deficiencies by age at cancer diagnosis. A sensitivity analysis was performed limiting the sample to only papillary and follicular thyroid cancers and the results were nearly identical.

Thyroid cancer survivors diagnosed at <40 years have an increased risk for several circulatory conditions (Table 2) when compared to the matched cancer-free population. The hypertension risks were significantly higher for thyroid cancer survivors diagnosed at <40 years in the adjusted HR 1-5 years after diagnosis (HR=2.03, 99% CI=1.75, 2.32 vs HR=1.58, 99% CI=1.48, 1.68). Both age groups had increased risks for heart disease 1-5 years after cancer diagnosis (HR=1.76, 99% CI=1.40, 2.21 vs HR=1.49, 99% CI=1.38,

1.60). Only hypertension remained significant across all three time periods in both age groups, while diseases of the circulatory system, heart, and veins and lymphatics remained significantly increased across all three time periods for the older age group.

Overall, thyroid cancer survivors had increased risks for other aging-related diseases (Table 3). Younger thyroid cancer patients had a statistically significantly increased risk of nutritional deficiencies in both the 1-5 year and >5-10 year follow-up periods. Increased risks of diabetes, disorders of lipid metabolism, eye disorders, ear conditions, diseases of the musculoskeletal system and connective tissue were observed for both age groups, throughout most of the follow-up periods.

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 one at baseline (Tables 4 and 5). 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 in the attributable risk fraction. 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.

Discussion

We conducted the first statewide assessment of age-related health conditions among thyroid cancer survivors and demonstrated the 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, cardiomyopathy, and nutritional deficiencies compared to age matched controls. Increased age at diagnosis and worse baseline health appeared to be significant contributors to the increased risk of multiple health problems.

There are several explanations for the elevated risks in younger survivors. We observed that younger thyroid cancer patients were more likely to receive RAI treatment, which has been previously associated with long-term health effects [15-17, 25]. TSH suppression therapy has been reported to be associated with adverse effects including osteoporosis, atrial fibrillation, and increased heart rate [26]. In a study population with a mean age of 61.6 years, 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 [27]. 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 our study, we did not observe increased risks due to these treatments in the younger population, but perhaps due to the smaller sample size of the younger patients, we did not have adequate power to detect risks. A possible explanation for young thyroid cancer survivors developing hypertension may be linked to anxiety and worry.

Thyroid cancer survivors have been reported to have increased rates of distress and worry, especially in younger survivors [28, 29].

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 [30, 31]. This increase in surveillance may help explain why the risk for osteoporosis was significantly increased for both age groups, however the risk pathological fractures was not. There may be a surveillance bias in survivors, which could lead to increased rates of osteoporosis. At the same time, younger cancer survivors have a disproportionately higher amount of cancer-related financial problems, which have been linked to delaying or forgoing medical care [32-34]. 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.

Many of the elevated risks we found in this study are not health conditions typically associated with patients less than 40 years of age, therefore it is even more crucial that healthcare providers are aware of these risks and are proactive about thyroid cancer survivors having regular follow-up as well as helping these patients lead a healthier lifestyle. It is important to address that age and baseline health were the driving factors for multiple circulatory health conditions and multiple other health conditions, which further increases the importance of a healthier lifestyle for thyroid cancer patients. However, it is also important to note that there was risk attributed to various treatments and this is also something that healthcare providers need to be aware of when looking at the long-term health of thyroid cancer survivors.

As the diseases we studied are diseases of aging, they were 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 in the context of diseases associated with 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. The majority of the risks decrease over time. This is likely due to the general population cohort being diagnosed with these diseases and health conditions as they age and catching up to the thyroid cancer survivors, not necessarily due a decrease in frequency of these diseases in the thyroid cancer survivors over time. Also, for the more specific diseases (CCS level 3 and 4), all prevalent cases were removed from analyses for each time period.

There are several limitations to this study. First, the study population of Utah is less diverse with low rates of alcohol consumption and smoking. However, this allowed for a more homogenous study population to try to assess treatment effects rather than the impact of lifestyle factors for long-term health effects. 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 dose of RAI and type of hormone therapy was not given. Hormone therapy could include hormone

replacement or hormone suppression, which likely have different effects on long-term health. Future studies to further assess the role of more specific treatments would be of interest.

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 [21, 22, 35-38], 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 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 five years after cancer diagnosis when cancer survivors are generally recommended to return to annual physical exams. 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, thyroid cancer survivors diagnosed before 40 years of age had higher risks that those diagnosed after 40. Some of the biggest risks were within the cardiovascular, endocrine, and musculoskeletal systems. There are multiple potential explanations for the elevated risks including surveillance bias, associated comorbidities, and treatment-associated side-effects. This study shows that there is likely a combination of these impacting the long-term health of thyroid cancer survivors. As we used population-level data in this study, it is good to identify these potential explanations for the long-term health effects, but it does not provide the in-depth data needed to speculate with regards to causality. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the Huntsman Cancer Institute, Cancer Control and Population Sciences Program (HCI Cancer Center Support Grant P30CA042014), and the NCRR grant, “Sharing Statewide Health Data for Genetic Research” (R01 RR021746, G. Mineau, PI) with additional support from the Utah State Department of Health and the University of Utah. We thank the Pedigree and Population Resource of the Huntsman Cancer Institute, University of Utah (funded in part by the Huntsman Cancer Foundation) for its role in the ongoing collection, maintenance and support of the Utah Population Database (UPDB). We thank the University of Utah Center for Clinical and Translational Science (CCTS) (funded by NIH Clinical and Translational Science Awards), the Pedigree and Population Resource, University of Utah Information Technology Services and Biomedical Informatics Core for establishing the Master Subject Index between the Utah Population Database, the University of Utah Health Sciences Center and Intermountain Healthcare.

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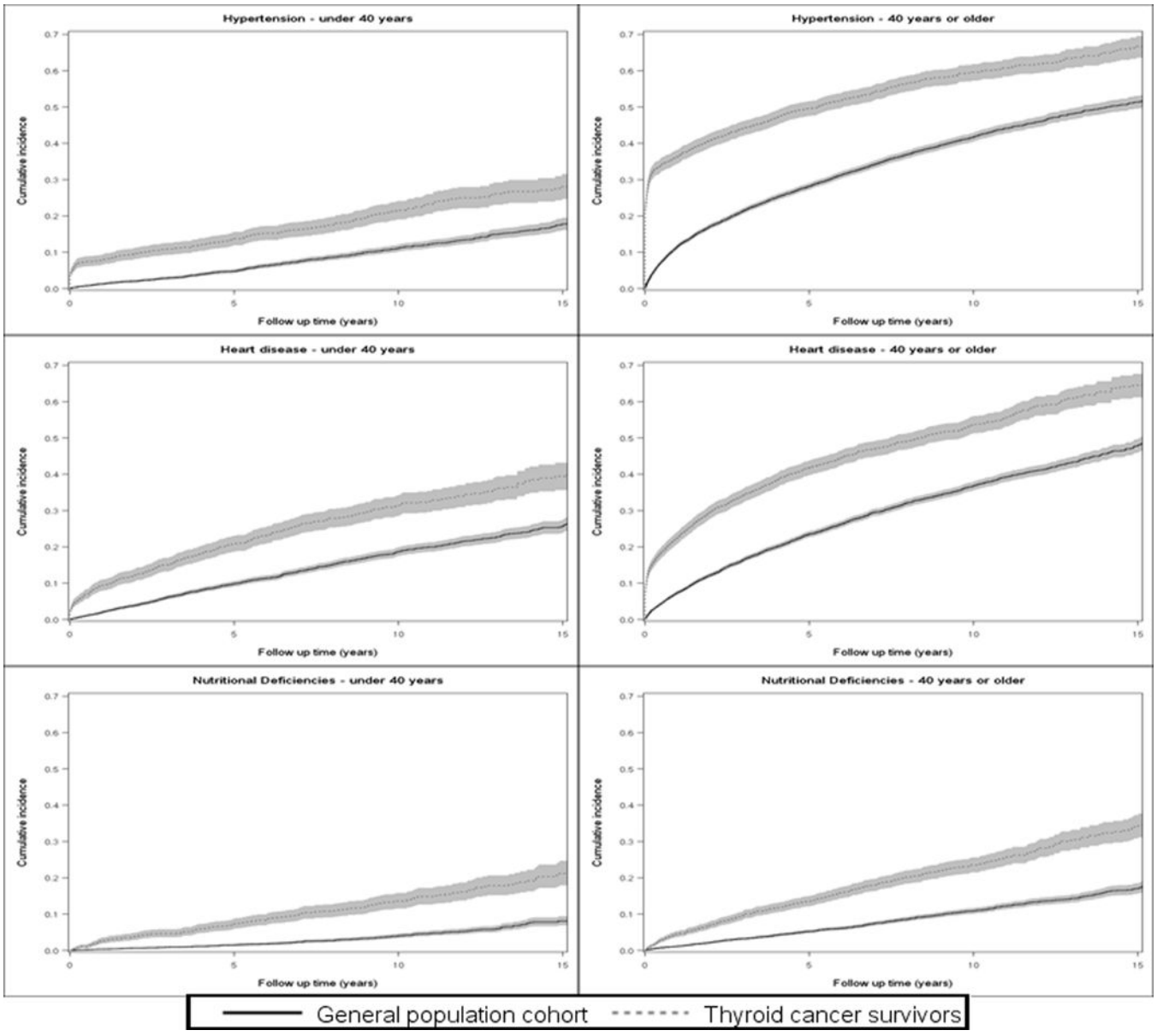

Figure 1.

Cumulative incidence curves for selected outcomes by age at thyroid cancer diagnosis for thyroid cancer survivors and the matched general population cohort

Table 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
Non-White	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	

	Thyroid cancer		Comparison group		
	N=3706	%	N=15587	%	P-value
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 one year prior to cancer diagnosis for survivor or for the index comparison cohort member

Table 2

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		>10 years after cancer diagnosis	
	Age < 40	Age ≥ 40	Age < 40	Age ≥ 40	Age < 40	Age ≥ 40
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Total number of circulatory system health conditions						
1	**1.50 (1.21, 1.85)**	**1.31 (1.15, 1.49)**	**1.50 (1.18, 1.90)**	1.08 (0.91, 1.27) *	1.17 (0.84, 1.64)	1.04 (0.79, 1.36)
2+	**2.25 (1.66, 3.05)**	**1.69 (1.49, 1.92)**	**1.47 (1.06, 2.06)**	**1.60 (1.37, 1.86)**	1.38 (0.93, 2.06)	**1.66 (1.32, 2.09)**
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)**	1.29 (0.99, 1.68)	**1.54 (1.28, 1.85)**
Hypertension	**2.03 (1.75, 2.32)** †	**1.58 (1.48, 1.68)** †*	**1.76 (1.30, 2.37)**	**1.39 (1.26, 1.51)** †	**1.63 (1.13, 2.35)**	**1.46 (1.18, 1.80)**
Diseases of the heart	**1.76 (1.40, 2.21)**	**1.49 (1.38, 1.60)** †	**1.39 (1.06, 1.84)**	**1.35 (1.15, 1.58)**	1.33 (0.92, 1.92)	**1.39 (1.09, 1.77)**
Heart valve disorders	1.96 (0.92, 4.21)	**1.47 (1.05, 2.06)**	1.37 (0.56, 3.35)	1.28 (0.98, 1.59) †	2.57 (0.94, 7.01)	1.32 (0.73, 2.40)
Congestive heart failure; nonhypertensive	10.55 (0.83, 134.09)	0.85 (0.55, 1.33)	2.72 (0.59, 12.55)	1.11 (0.67, 1.83)	5.05 (0.49, 51.78)	1.03 (0.47, 2.27)
Peri-; endo-; and myocarditis; cardiomyopathy	**9.16 (1.45, 58.00)**	1.03 (0.58, 1.85) *	1.96 (0.43, 8.91)	1.46 (0.70, 3.03)	3.85 (0.26, 57.67)	1.63 (0.66, 4.00)
Cardiomyopathy	17.44 (0.53, 574.86)	0.84 (0.40, 1.76)	1.36 (0.09, 20.28)	1.04 (0.40, 2.67)	7.46 (0.31, 181.12)	1.48 (0.48, 4.56)
Other peri-; endo-; and myocarditis	**8.49 (1.10, 65.28)**	1.60 (0.69, 3.72)	2.32 (0.40, 13.43)	2.39 (0.82, 6.96)	1.96 (0.07, 52.57)	1.87 (0.47, 7.51)
Nonspecific chest pain	**1.62 (1.12, 2.33)**	**1.72 (1.36, 2.17)**	1.12 (0.71, 1.75)	1.19 (0.84, 1.69)	1.36 (0.72, 2.59)	**1.39 (1.08, 1.71)** †
Pulmonary heart disease	0.91 (0.20, 4.15)	1.29 (0.83, 2.00)	0.90 (0.22, 3.75)	1.27 (0.76, 2.14)	2.01 (0.47, 8.51)	1.82 (0.89, 3.75)
Cardiac dysrhythmias	1.50 (0.95, 2.38)	**1.55 (1.20, 1.99)**	**1.67 (1.03, 2.71)**	1.11 (0.79, 1.55)	1.29 (0.63, 2.66)	1.18 (0.71, 1.96)
Atrial fibrillation		1.05 (0.66, 1.66)	0.81 (0.06, 10.39)	1.19 (0.70, 2.03)	5.21 (0.49, 55.92)	1.81 (0.96, 3.41)
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)	1.18 (0.27, 5.17)	1.28 (0.73, 2.24)
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)**	1.29 (0.79, 2.12)	1.19 (0.85, 1.65)
Peripheral and visceral atherosclerosis	3.70 (0.40, 34.29)	1.42 (0.89, 2.27)	2.40 (0.25, 22.99)	1.29 (0.74, 2.23)	1.24 (0.27, 5.76)	0.76 (0.30, 1.91)
Hypotension	**3.05 (1.32, 7.03)**	1.16 (0.73, 1.85) *	2.15 (0.75, 6.20)	1.02 (0.58, 1.80)	**1.97 (1.12, 2.83)** †	1.18 (0.55, 2.52)
Diseases of veins and lymphatics	**1.60 (1.12, 2.28)**	**1.58 (1.35, 1.85)**	1.28 (0.92, 1.65) †	**1.45 (1.20, 1.76)**	1.10 (0.67, 1.81)	**1.31 (1.03, 1.59)** †
Phlebitis; thrombophlebitis and thromboembolism	1.89 (0.73, 4.89)	**2.02 (1.37, 2.98)**	1.92 (0.84, 4.37)	1.50 (0.92, 2.45)	1.37 (0.46, 4.06)	0.68 (0.26, 1.77)
Varicose veins of lower extremity	2.08 (0.68, 6.37)	1.32 (0.64, 2.74)	0.87 (0.14, 5.37)	1.12 (0.49, 2.60)	1.81 (0.23, 14.06)	1.55 (0.50, 4.79)
Hemorrhoids	1.33 (0.79, 2.24)	**1.55 (1.23, 1.95)**	1.50 (0.88, 2.54)	1.42 (1.05, 1.91)	0.82 (0.39, 1.71)	1.63 (1.01, 2.63)

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

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

† Proportional hazard assumption not meant; flexible spline model used

Table 3

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		>10 years after cancer diagnosis	
	Age < 40	Age ≥ 40	Age < 40	Age ≥ 40	Age < 40	Age ≥ 40
	n=3706	n=15587	n=2821	n=10085	n=1331	n=4254
	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)	HR (99% CI)
Total number of other health conditions						
1	**1.46 (1.20, 1.79)**	1.07 (0.90, 1.27) *	1.02 (0.78, 1.34)	0.85 (0.67, 1.09)	1.46 (0.45, 4.69)	0.70 (0.19, 2.52)
2+	**1.51 (1.30, 1.75)**	**1.73 (1.58, 1.90)**	**1.54 (1.30, 1.83)**	**1.57 (1.41, 1.76)**	**1.48 (1.17, 1.87)**	**1.42 (1.19, 1.69)**
Diabetes mellitus without complication	**1.97 (1.63, 2.31)** †	**1.66 (1.39, 1.97)**	**2.20 (1.48, 3.26)**	**1.42 (1.17, 1.73)**	**2.19 (1.36, 3.51)**	**1.36 (1.02, 1.80)**
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)	1.33 (0.52, 3.45)	1.30 (0.77, 2.21)
Nutritional deficiencies	**4.77 (3.01, 7.56)**	**2.26 (1.80, 2.84)** *	**2.93 (2.52, 3.35)** †	**1.72 (1.31, 2.25)** *	**2.24 (1.31, 3.82)**	**1.86 (1.29, 2.68)**
Disorders of lipid metabolism	**1.92 (1.62, 2.21)** †	**1.59 (1.41, 1.80)**	**1.78 (1.27, 2.47)**	**1.34 (1.15, 1.56)**	**1.74 (1.15, 2.63)**	**1.29 (1.03, 1.62)**
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)	**4.20 (1.09, 16.17)**	0.53 (0.24, 1.17)
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)**	1.52 (0.99, 2.32)	**1.38 (1.12, 1.63)** †
Cataract	0.27 (0.01, 7.62)	**1.46 (1.09, 1.95)**	0.48 (0.03, 7.30)	1.00 (0.69, 1.46)	3.85 (0.86, 17.16)	1.51 (0.89, 2.57)
Glaucoma	10.00 (0.17, 595.08)	1.16 (0.55, 2.45)		0.98 (0.38, 2.54)		2.50 (0.71, 8.77)
Blindness and vision defects	**1.65 (1.01, 2.67)**	**1.43 (1.03, 1.99)**	0.72 (0.36, 1.44)	1.35 (0.90, 2.02)	1.25 (0.51, 3.08)	**1.50 (1.08, 1.92)** †
Ear conditions	**1.32 (1.06, 1.66)**	**1.68 (1.53, 1.82)** †	**1.37 (1.03, 1.81)**	**1.50 (1.22, 1.84)**	1.30 (0.88, 1.92)	**1.78 (1.31, 2.42)**
Diseases of the musculoskeletal system and connective tissue	**1.45 (1.26, 1.67)**	**1.59 (1.51, 1.67)** †	**1.34 (1.13, 1.59)**	**1.49 (1.33, 1.68)**	**1.28 (1.01, 1.62)**	1.16 (0.97, 1.40)
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)	2.71 (0.35, 21.10)	1.86 (0.57, 6.04)
Non-traumatic joint disorders	**1.56 (1.28, 1.90)**	**1.37 (1.34, 1.40)** †	**1.38 (1.09, 1.74)**	**1.42 (1.23, 1.63)**	1.34 (0.99, 1.82)	1.19 (0.95, 1.48)
Rheumatoid arthritis and related disease	1.56 (0.45, 5.39)	0.94 (0.45, 2.00)	0.78 (0.19, 3.31)	1.28 (0.60, 2.75)	2.10 (0.38, 11.57)	2.52 (0.73, 8.67)
Osteoarthritis	1.14 (0.61, 2.16)	**1.49 (1.19, 1.87)**	1.34 (0.76, 2.34)	1.30 (0.99, 1.71)	0.95 (0.46, 1.93)	1.28 (0.79, 2.07)
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)**	1.30 (0.93, 1.81)	1.14 (0.88, 1.49)
Osteoporosis	**7.56 (1.99, 28.78)**	**2.13 (1.91, 2.35)** †	**2.86 (1.93, 3.80)** †	**2.19 (1.65, 2.92)**	2.10 (0.53, 8.32)	**1.68 (1.09, 2.58)**
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)	3.07 (0.58, 16.30)	1.26 (0.45, 3.56)
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)	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 within follow-up periods p-value <0.01

† Proportional hazard assumption not meant; flexible spline model used

Table 4

Risk Factors and attributable fraction for multiple circulatory system health conditions

	All			< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Treatment[1]									
Surgery only		Reference			Reference			Reference	
Surgery and RAI	1.13	(0.99, 1.29)	0.06	1.08	(0.76, 1.55)	0.04	1.14	(0.98, 1.31)	0.06
Hormone Therapy[1]									
No		Reference			Reference			Reference	
Yes	**1.19**	**(1.02, 1.39)**	0.04	1.01	(0.66, 1.54)	0.00	**1.21**	**(1.02, 1.43)**	0.05
Cancer stage at diagnosis[1]									
Localized		Reference			Reference			Reference	
Regional/Distant	0.98	(0.84, 1.14)	0.00	0.96	(0.64, 1.44)	0.00	0.99	(0.84, 1.17)	0.00
Age at cancer diagnosis[2]									
< 30		Reference			Reference			Reference	
30-39	**1.68**	**(1.12, 2.52)**	0.04	**1.63**	**(1.07, 2.46)**	0.29			
40-49	**2.84**	**(1.93, 4.18)**	0.12					Reference	
50-59	**4.16**	**(2.84, 6.09)**	0.19				**1.47**	**(1.20, 1.80)**	0.09
60-69	**6.78**	**(4.61, 9.98)**	0.19				**2.40**	**(1.94, 2.96)**	0.15
70+	**11.27**	**(7.62, 16.67)**	0.18				**3.98**	**(3.18, 4.98)**	0.17
Diagnosis year[3]									
1997-2000		Reference			Reference			Reference	
2001-2004	1.10	(0.86, 1.42)	0.03	1.90	(0.92, 3.91)	0.11	1.00	(0.76, 1.31)	0.00
2005-2008	1.15	(0.91, 1.46)	0.01	**2.16**	**(1.07, 4.33)**	0.18	1.02	(0.79, 1.31)	0.01
2009-2012	0.89	(0.70, 1.13)	0.00	1.72	(0.86, 3.46)	0.15	0.89	(0.61, 1.01)	0.00
Gender[4]									
Female		Reference			Reference			Reference	

	All			< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Male	**1.67**	**(1.45, 1.93)**	0.12	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	1.20	(0.57, 2.54)	0.00	1.31	(0.48, 3.60)	0.01	1.14	(0.37, 3.57)	0.00
18-24.9 kg/m^2		Reference			Reference			Reference	
25-29.9 kg/m^2	**1.19**	**(1.02, 1.40)**	0.06	1.15	(0.74, 1.80)	0.03	**1.20**	**(1.01, 1.42)**	0.07
30+ kg/m^2	**1.48**	**(1.23, 1.77)**	0.08	1.48	(0.90, 2.44)	0.06	**1.48**	**(1.22, 1.79)**	0.09
Charlson Comorbidity Index[6]									
0		Reference			Reference			Reference	
1+	**2.28**	**(1.97, 2.63)**	0.31	**2.86**	**(1.98, 4.14)**	0.26	**2.19**	**(1.87, 2.55)**	0.32
Number of Cancer[7]									
1		Reference			Reference			Reference	
2+	0.97	(0.77, 1.22)	0.00	1.05	(0.56, 1.95)	0.00	0.96	(0.75, 1.22)	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, age at diagnosis, year of diagnosis, BMI at baseline, CCI at baseline, and race

Table 5

Risk Factors and attributable fraction for multiple other health conditions

	All			< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Treatment[1]									
Surgery only		Reference			Reference			Reference	
Surgery and RAI	**1.12**	**(1.02, 1.23)**	0.06	0.96	(0.80, 1.15)	0.00	**1.18**	**(1.06, 1.31)**	0.08
Hormone Therapy[1]									
No		Reference			Reference			Reference	
Yes	**1.29**	**(1.16, 1.43)**	0.06	1.17	(0.94, 1.45)	0.04	**1.29**	**(1.14, 1.46)**	0.06
Cancer stage at diagnosis[1]									
Localized		Reference			Reference			Reference	
Regional/Distant	0.97	(0.87, 1.08)	0.00	0.98	(0.80, 1.20)	0.00	0.98	(0.86, 1.11)	0.00
Age at cancer diagnosis[2]									
< 30		Reference			Reference				
30-39	**1.27**	**(1.05, 1.55)**	0.04	**1.25**	**(1.02, 1.52)**	0.14			
40-49	**1.70**	**(1.40, 2.05)**	0.09					Reference	
50-59	**2.48**	**(2.05, 3.00)**	0.15				**1.46**	**(1.28, 1.67)**	0.11
60-69	**2.96**	**(2.42, 3.63)**	0.11				**1.76**	**(1.51, 2.04)**	0.10
70+	**3.18**	**(2.54, 3.97)**	0.07				**1.90**	**(1.59, 2.27)**	0.07
Diagnosis year[3]									
1997-2000		Reference			Reference			Reference	
2001-2004	**1.20**	**(1.02, 1.43)**	0.03	1.15	(0.83, 1.59)	0.03	1.21	(0.99, 1.48)	0.03
2005-2008	**1.30**	**(1.10, 1.52)**	0.07	**1.40**	**(1.03, 1.90)**	0.09	**1.24**	**(1.03, 1.50)**	0.06
2009-2012	**1.18**	**(1.01, 1.38)**	0.06	1.28	(0.94, 1.72)	0.08	1.13	(0.94, 1.36)	0.05
Gender[4]									
Female		Reference			Reference			Reference	

	All			< 40			≥ 40		
	HR	**95% CI**	**AF**	**HR**	**95% CI**	**AF**	**HR**	**95% CI**	**AF**
Male	1.07	(0.96, 1.19)	0.01	**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	0.87	(0.55, 1.37)	0.00	0.89	(0.50, 1.59)	0.00	0.87	(0.41, 1.83)	0.00
18-24.9 kg/m^2		Reference			Reference			Reference	
25-29.9 kg/m^2	1.10	(0.99, 1.23)	0.03	0.99	(0.79, 1.25)	0.00	1.12	(0.99, 1.26)	0.04
30+ kg/m^2	**1.17**	**(1.03, 1.33)**	0.03	1.30	(0.99, 1.71)	0.03	**1.15**	**(1.00, 1.33)**	0.03
Charlson Comorbidity Index[6]									
0		Reference			Reference			Reference	
1+	**2.12**	**(1.92, 2.34)**	0.24	**2.51**	**(2.06, 3.06)**	0.19	**2.01**	**(1.80, 2.25)**	0.25
Number of Cancer[7]									
1		Reference			Reference			Reference	
2+	0.94	(0.81, 1.10)	0.00	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, age at diagnosis, year of diagnosis, BMI at baseline, CCI at baseline, and race