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Diagnostic Procedures Using Radiation and Risk of Thyroid Cancer: Causal Association or Detection Bias? An Examination of Population Cancer Trends and Data from the NYC Fire Department

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Diagnostic Procedures Using Radiation and Risk of Thyroid Cancer: Causal Association or Detection Bias? An Examination of Population Cancer Trends and Data from the NYC Fire Department

by

Rachel Zeig-Owens

A dissertation submitted to the Graduate Faculty in Public Health in partial fulfillment of the requirements for the degree of Doctor of Public Health, The City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Public Health in satisfaction of the dissertation requirement for the degree of Doctor of Public Health.

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THE CITY UNIVERSITY OF NEW YORK
Abstract
Diagnostic Procedures Using Radiation and Risk of Thyroid Cancer: Causal Association or Detection Bias? An Examination of Population Cancer Trends and Data from the NYC Fire Department
by
Rachel Zeig-Owens
Advisor: Lorna Thorpe

Background: Thyroid cancer (TC) is a common cancer diagnosis in the United States, whose incidence is increasing. Disaster and radiation treatment studies show high doses of radiation can cause TC. Some diagnostic procedures, whose use is increasing, expose individuals to low-dose radiation but can also incidentally detect subclinical TC. Evidence regarding low-dose radiation risk is limited.

Objectives: To investigate the possible association of greater use of diagnostic procedures with TC, either causally through radiation exposure or via incidental detection.

Methods: Two data sources were used: National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) data and Fire Department of the City of New York (FDNY) data. Using age-period-cohort analyses of SEER data (1973-2011), trends in TC incidence in the United States were decomposed into the effects of age, period and cohort in the context of changes in diagnostic procedures. Using FDNY data, the association of radiation exposure from diagnostic procedures with TC risk was assessed. Whether heightened medical attention (screening using diagnostic procedures and number of medical exams) mediated the previously-observed association between World Trade Center (WTC) exposure and TC was also investigated.
Results: Between 1973 and 2011, TC incidence has increased and mortality has remained stable. Independent age, period and cohort effects were observed for TC incidence in the United States. Risk increased around the 1993-1997 period, consistent with hypotheses of increased detection via diagnostic procedures, and decreased around the 1970s birth cohort. Analyses by cancer subtypes and tumor size showed mostly similar results.

Among firefighters, radiation exposure from diagnostic procedures and TC was not statistically significant (adjusted hazard ratio [HR]=1.02 per mSv), although after adjusting for confounders, the highest radiation exposure category ≥10.1 mSv, had a HR of 1.91, 95% confidence interval (CI) 0.55-5.18. TC risk was higher among firefighters with WTC exposure on 9/11/2001 but not after age-adjustment (HR=1.75, 95% CI 0.80-3.82). The association was partially mediated by heightened medical attention; 21.9% of the association was due to screening diagnostic procedures and medical exams.

Conclusions: Incidental detection of TC may be contributing to the increasing incidence and possibly exposure to low-dose radiation from diagnostic procedures as well.
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Chapter 1: Introduction

1.1. Thyroid Cancer in the United States

Currently, thyroid cancer is the 11th most common cancer diagnosed in the United States.\textsuperscript{1} Since the 1970s when United States cancer rates began to be tracked, the incidence rate for thyroid cancer has increased nearly three-fold; the annual age-adjusted incidence increased from 4.8 per 100,000 persons in 1973-1977 to 12.9 per 100,000 persons in 2007-2011.\textsuperscript{1} During this time the median age at diagnosis of thyroid cancer increased slightly from 45 in 1973-1977 to 50 in 2007-2011.\textsuperscript{2} The majority of cases diagnosed in the country are among females, with current incidence among females being three times higher than among males (annual incidence rate during 2007-2011 of 19.1 per 100,000 versus 6.4 per 100,000, respectively).\textsuperscript{1} Additionally, in the United States, non-Hispanic whites have higher incidence rates of thyroid cancer than other racial/ethnic groups. For example, the rate among non-Hispanic whites in 2007-2011 was 14.4 per 100,000 compared with 7.6 per 100,000 among blacks. While thyroid cancer incidence has increased differentially by demographic group over time, the mortality rate associated with thyroid cancer has been relatively stable, at approximately 0.5 per 100,000 for both females and males and all racial/ethnic groups since the 1970s.

This trend is not unique to the United States. Many countries worldwide have observed an increase in thyroid cancer incidence over the last couple of decades.\textsuperscript{3-7} For example, in Italy, from 1991 to 2005 the incidence rate increased from 8.2 per 100,000 to 17.6 per 100,000.\textsuperscript{6}
There are four main subtypes of thyroid cancer, papillary carcinoma, follicular carcinoma, medullary carcinoma and anaplastic carcinoma. Most thyroid cancer cases in the United States are papillary carcinomas. The rise in thyroid cancer incidence since the 1970s in the United States has been largely driven by increased diagnoses of non-fatal papillary carcinomas. The 5-year survival rate for papillary carcinomas is nearly 100%. However, for anaplastic carcinomas, which have had a consistent incidence rate of 0.1 per 100,000 in the United States in recent decades, the 5-year survival rate less than 10% and in many cases the median survival time is three months.

1.2. Major Known Causes of Thyroid Cancer

Few causal factors have been identified for thyroid cancer. Exposure to ionizing radiation is the main known cause of thyroid cancer. Exposure to high doses of radiation (great than 100 mSv) from medical treatments and nuclear disasters, particularly among children, has consistently been found to be associated with increased risk of developing thyroid cancer. And, it has been observed among World War II atomic bomb survivors that the relationship between radiation exposure and thyroid cancer is linear however, the level of radiation in this population was high for most. Risks associated with exposure to low doses of radiation, for example during diagnostic procedures with doses less than 10 mSv on average, remain unclear. Most studies investigating risks of radiation exposure from diagnostic procedures during adulthood have relied on self-reported exposure measures and typically examine exposure to X-rays only, which expose individuals to radiation doses lower than CT scans. Many of these studies reported small non-significant elevations in risk and were subject to measurement error and recall bias in particular. However, a recent 2013 study found that individuals exposed to
computer tomography (CT) scans as a child had a significant increased risk of thyroid cancer compared with those unexposed.\textsuperscript{20} To date, no meta-analyses have been conducted to investigate the association of low dose radiation exposure with thyroid cancer.

Other than radiation exposure, other causes of thyroid cancer are not well established.\textsuperscript{21} There is some evidence that family history of thyroid cancer, particularly for some subtypes of thyroid cancer, is associated with an increased risk of thyroid cancer.\textsuperscript{21,22} However, it is also possible that environmental factors experienced collectively by a family are truly associated with thyroid cancer.\textsuperscript{22} Recent studies though suggest a genetic component to thyroid cancer exists.\textsuperscript{23,24} Hormonal changes related to female reproduction have also been considered a possible risk factor for thyroid cancer. However, results from 14 pooled studies investigating this showed factors associated with menopause and reproduction, such as age at first pregnancy or number of pregnancy, were either not significantly associated with thyroid cancer or the association was small.\textsuperscript{25} For example, the odds ratio for thyroid cancer was 1.2 (95\% CI 1.0-1.4) among women with at least one birth compared with none.\textsuperscript{25} The role of thyroid stimulating hormone (TSH) in thyroid cancer development is still being investigated. Some have shown through genetic studies that low levels of TSH is associated with thyroid cancer but a meta-analysis from 2012 concluded higher levels of TSH was related to thyroid cancer risk.\textsuperscript{26,27} While it is possible that both high and low levels of TSH cause thyroid cancer, this association is currently unknown.\textsuperscript{11,26-28} Other studies have suggested that iodine intake, a history of goiters, higher body weight, smoking and alcohol consumption are associated with thyroid cancer however others have found no association.\textsuperscript{11,21,29-40}
1.3. Description of Incidental Detection of Thyroid Cancer

In addition to the possibility of radiation exposure during diagnostic procedures contributing to the increase in thyroid cancer incidence, one other plausible explanation for the recent rise in thyroid cancer is that medical advancements in diagnostic procedures (both involving and not involving radiation) have improved detection and enable the diagnosis of what would have otherwise been undiagnosed thyroid cancer.\textsuperscript{41-43} For example, asymptomatic thyroid cancer too small to be detected by palpitation (tumors less than 2 cm) can now be diagnosed through the use of ultrasound or CT scans. In many instances these thyroid cancers, sometimes as small as 2 mm, can be detected during diagnostic procedures for other unrelated medical conditions or even during routine medical exams.\textsuperscript{44-46} It is estimated that during a CT scan thyroid nodules are incidentally detected up to 17\% of the time,\textsuperscript{47-52} resulting in a potential diagnosis of cancer that may otherwise have been diagnosed later or never diagnosed. Additionally, a 2014 study found among individuals randomized to receive chest CT scans the rate of thyroid cancer was 2.19 times higher than those who did not receive the scans and concluded the difference was a result of incidental detection.\textsuperscript{46} Further, a 1985 study found among 101 individuals autopsied over a third had thyroid cancer that had never been diagnosed.\textsuperscript{53} In 2010 in the United States, an estimated 148 CT scans per 1,000 persons were conducted.\textsuperscript{54} This is nearly three times the number of CT scans conducted in the decade prior.\textsuperscript{54,55} A similar increase in use was also observed for ultrasounds during this period.\textsuperscript{54} As diagnostic procedures have improved and use has increased in frequency in the United States, asymptomatic cases that may have gone undetected a few decades ago are now being detected incidentally.\textsuperscript{43-45}

1.4. Summary and Gaps in Current Literature
While many studies in the United States, as well as globally, have documented the rise in thyroid cancer rates, period and cohort effects have not been investigated separately by sex. This assessment may help determine the reason for the differential increases, both overall and by sex, over the last four decades, which has yet to be adequately explained. One potential explanation is increased radiation exposure from diagnostic procedures. The association between radiation exposure and thyroid cancer is known among those exposed to high doses and most importantly during childhood. However, to date, the risk of thyroid cancer following exposure to low doses of radiation has not been clearly shown. Another potential non-casual reason for the escalating rate of thyroid cancer is incidental detection of tumors that would have otherwise gone undiagnosed. The findings from this dissertation aim to better characterize the sex-specific pattern of increasing incidence over time in the context of changes in use of low dose radiation diagnostic procedures, explore the possible causal relationship between low dose radiation exposure from diagnostic procedures and risk for developing thyroid cancer, as well assess the potential role for incidental detection due to heightened medical attention in driving these increases.

1.5. Overview of the Dissertation

1.5.1. Overall Goals

The purpose of this dissertation was to investigate the possible association between increased use of diagnostic procedures and the incidence of thyroid cancer; this association may be causal through radiation exposure or may be through incidental detection. To understand this relationship, the increasing trend of thyroid cancer incidence in the United States was first characterized using age-period-cohort analysis techniques to ascertain whether distinct period
effects could be discerned, and whether those period effects generally corresponded to shifts in diagnostic procedure use. Then, using a cohort of Fire Department of the City of New York (FDNY) firefighters, the association between exposure to radiation from diagnostic procedures and thyroid cancer was evaluated. Finally, within the same firefighter cohort, the influence of incidental detection of thyroid cancer on a previously observed association between World Trade Center and thyroid cancer was assessed.

1.5.2. Specific Aims

The specific aims for this dissertation were:

Aim 1: Examine the trend in thyroid cancer incidence in the United States between 1/1/1973 and 12/31/2011 by age, period and cohort.

a) Examine the trend among all thyroid cancers in the United States

b) Examine the trend by race, type of tumor and size of tumor.

Hypothesis 1: The increase in thyroid cancer incidence in the United States is a result of a period effect, reflecting shifts in detection and screening in the late 1990s.

Aim 2: Estimate the incidence rate of thyroid cancer among firefighters between 9/11/2001 and 12/31/2013 and assess the association between exposure to radiation from diagnostic procedures and incidence thyroid cancer.

Hypothesis 2: Firefighters with higher levels of radiation from diagnostic procedures will have a higher incidence of thyroid cancer compared with firefighters with lower levels of radiation from diagnostic procedures after controlling for possible confounders such as age, number of FDNY medical exams, smoking status and World Trade Center exposure.
**Aim 3:** Assess whether the previously observed association between World Trade Center exposure and thyroid cancer diagnoses is mediated through increased medical attention (a potential detection bias).

_Hypothesis 3:_ The association between World Trade Center exposure and thyroid cancer is mediated by incidental detection during both computerized tomography scans and medical exams.

### 1.5.3. Organization of the Dissertation

This dissertation includes four more chapters. In Chapter 2, additional background regarding thyroid cancer in the United States over nearly four decades is provided. The United States trends in thyroid cancer are described in terms of changes in age groups, calendar periods and birth cohorts (Aim 1). Secondary analyses are also provided investigating the trends by race, subtypes of thyroid cancer and the size of tumor. Analyses assessing radiation exposure from diagnostic procedures and the risk of thyroid cancer among FDNY firefighters (Aim 2) are presented in Chapter 3. In Chapter 4, findings are presented from the mediation analysis investigating the role medical attention played in the relationship between World Trade Center exposure and thyroid cancer (Aim 3). A summary of the findings from Chapters 2 through 4 is included in Chapter 5. In this chapter the public health relevance of the studies is also discussed and policy recommendations are made.

### 1.5.4. Significance of the Dissertation

Results from these aims describe in detail trends in thyroid cancer incidence nationally and
explore possible reasons for the observed increase in incidence such as the increased use of diagnostic procedures. Specifically, analyses of trends in thyroid cancer incidence by subtype of thyroid cancer and by size of the tumor at diagnosis help ascertain potential the reasons for observed increases over time. Additionally, this research provides insight into potential thyroid cancer risks related to widely used diagnostic procedures such as CT scans. Analysis of medical access data from FDNY enables a better understanding of whether this thyroid cancer risk from diagnostic procedures is causal due to radiation exposure or non-causal due to incidental detection, which can inform prevention strategies. Finally, the causal framework used to examine mediation in survival data can be applied to other outcomes when assessing detection bias such as in a World Trade Center exposure analysis.

1.6. Data Sources and Study Populations

1.6.1. Data Sources and Study Populations for Aim 1

Two data sources were used for Aim 1. For the primary analyses and most of the secondary analyses incident cases of thyroid cancer (n=66,359) by sex and 5-year age groups diagnosed between 1/1/1973 and 12/31/2011 were obtained from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) 9 data. These data include cancer cases from nine SEER cancer registries in the United States (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah). Population estimates using United States Census data were also obtained from the SEER 9 data by sex and 5-year age groups for the population in the nine geographic regions that represented in SEER 9. The SEER 9 data represents just over 9% of the United States population. Thyroid cancer deaths (n=32,804) by sex and 5-year age groups occurring between 1/1/1973 and 12/31/2011
were obtained from SEER data using data provided by the National Center for Health Statistics. These data include all deaths within the United States, not just the nine SEER cancer registry geographic regions. United States Census data for the whole country were also obtained from SEER data to analyze mortality rates. For this study, all data were restricted to 20-79 years of age.

1.6.2. Data Sources and Study Populations for Aims 2 and 3

The study population for Aims 2 and 3 was selected from the FDNY employee records, which includes hire date, race, sex, and date of birth. The source population included firefighters who were active (i.e., not retired) on 9/11/2001 or who were hired between 9/11/2001 and the end of the study, 12/31/2013. Firefighters with a history of cancer before the start of follow-up were excluded (n=137). Non-white firefighters (n=1,552) and females firefighters (n=41) were also excluded because of small numbers and well-documented differences in incidence rates in the United States. The final study population included 14,724 white, male firefighters.

Diagnostic procedure data was obtained from the FDNY medical records and the dose of radiation was estimated for each type of procedure. Estimated doses were based on published national averages for the various procedures, which included chest X-rays, chest CT scans, sinus CT scans, and PET scans. The dates of FDNY medical exams and thyroid cancer diagnoses were also obtained from the FDNY medical records. Cancer diagnoses were confirmed either by matches to state cancer registries or by review of medical records from a treating physician. In addition to FDNY medical record data, World Trade Center exposure status and health behaviors
such as smoking status were collected from the FDNY self-administered health questionnaire data.
2.1. Introduction

Thyroid cancer is one of the most common cancers in the United States and its occurrence has been rising. Since the 1970s incidence has nearly tripled; the annual age-adjusted incidence increased from 4.8 per 100,000 persons in 1973-1977 to 12.9 per 100,000 in 2007-2011, the most current years for which data are available.\textsuperscript{1} The majority of the thyroid cancer cases have been diagnosed in females throughout this time, but the gender disparity has been slightly widening in recent years; currently, the age-adjusted incidence rate among males is a third of the incidence rate among females (6.4 per 100,000 verses 19.1 per 100,000 respectively).\textsuperscript{1} Additionally, the rate of thyroid cancer varies by race/ethnicity with non-Hispanic whites consistently having the highest incidence rate since national cancer rates were documented. Four main subtypes of thyroid cancer are papillary carcinoma, follicular carcinoma, medullary carcinoma and anaplastic carcinoma. The rise in thyroid cancer incidence has been largely driven by increases in papillary tumors, which have a 5-year survival rate of nearly 100\% for non-metastatic cancers.\textsuperscript{2,3} The 5-year survival rate for anaplastic carcinomas, which have an incidence rate of 0.1 per 100,000 and have not been increasing, is less than 10\% and in many cases the median survival time is three months.\textsuperscript{2,4} Thus, while incidence has increased over the last four decades, mortality has remained fairly constant since the 1970s, at about 0.5 per 100,000 annually for both females and males and all race/ethnicities.\textsuperscript{1} Over the last couple of decades, a similar pattern of increasing incidence and stable mortality has been observed worldwide for thyroid cancer.\textsuperscript{5-11}
While the trend in the United States of an increase in incidence, but not mortality, has been well documented, the reasons for this remain uncertain. \(^3,12-15\) Exposure to ionizing radiation at high doses has been shown to be a major cause of thyroid cancer, particularly among those exposed during childhood. \(^16,17\) Other causes of thyroid cancer are not well established. \(^18,19\) Family history of thyroid cancer, mainly for some subtypes of thyroid cancer, is believed to be associated with an increased risk of thyroid cancer and genome-wide association studies have supported this. \(^18,20,21\) Based on the female to male ratio of thyroid cancer diagnoses, hormonal influences are possible but more research involving the hormonal relationship, specifically the thyroid-stimulating hormone (TSH), with thyroid cancer is needed. \(^22\) Currently, low levels of TSH \(^23\) as well as high levels \(^24\) have been found to be associated with thyroid cancer risk. Some research has suggested that iodine deficiency, higher body weight, smoking, and alcohol consumption are associated with thyroid cancer however others have not found these associations. \(^22,25-35\)

In addition to increasing thyroid cancer rates during the last few decades, since the 1980s this period has also seen technological improvements and increased use of diagnostic procedures involving ionizing radiation, such as computer tomography (CT) scans, and diagnostic procedures without radiation, such as ultrasounds. \(^36-38\) In the United States, using health care market data collected from surveys of over 2000 hospitals and imagining centers, it is estimated that CT scan use increased from nearly no CT scans per year in the early 1980s to more than 10 million CT scans per year in 1990. Over the next 16 years (1991-2006), the number of CT scans rose to more than 60 million CT scans per year \(^38\) and currently 80 million CT scans are conducted every year. \(^39\) Similar increases of ultrasounds during this time have been observed in populations belonging to large healthcare groups. \(^37\) Through the use of these diagnostic
procedures, asymptomatic thyroid cancer tumors, too small to be detected by palpitation (tumors less than 2 cm), can now be diagnosed during tests for other unrelated medical conditions or even during routine medical exams, prompting concern that the rise in thyroid cancer incidence may be related to increasing use of diagnostic procedures.\textsuperscript{8,40-43}

Decomposition of the trends in thyroid cancer by age, period, and cohort provides a means of assessing the possibility of period-based influences contributing to the rising incidence of thyroid cancer, such as the advent and uptake of diagnostic procedures. An increase due to incidental diagnosis should be evident as a calendar period effect dating to the introduction of CT scanners in the 1980s, the same time ultrasound use also began to rise.\textsuperscript{36,37,44} One previous age-period-cohort examination of thyroid cancer in the United States dates from before the widespread use of CT scans and only considered incidence in the state of Connecticut between 1935 and 1992, while other two studies examining more recent trends did not formally compare the role of period and cohort.\textsuperscript{45-47} Some age-period-cohort studies from other countries have observed a calendar period effect and suggest the increase in incidence was due to improvements in detection.\textsuperscript{5,7} The aim of this present study was to examine trends in thyroid cancer incidence in the United States from 1973 to 2011 using age-period-cohort analyses to assess the extent to which a calendar period effect could be observed that was potentially related to increased use of certain diagnostic tests. We conducted secondary analyses to determine if the observed results were similar by race, type of tumor and size of tumor and also to establish if trends in thyroid cancer mortality rates were similar.
2.2. Methods

2.2.1. Data source

Incidence data

Thyroid cancer cases (ICD-O-3 site code C739) by sex and 5-year age groups diagnosed between 1/1/1973 and 12/31/2011 were obtained from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) 9 data. These data include cancer cases from nine SEER cancer registries in the United States (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah). Population estimates by sex and 5-year age groups for the SEER 9 population from the United States Census data were also obtained from the SEER 9 data. The SEER 9 data represents just over 9% of the United States population. Data sets representing a larger proportion of the United States do not include cancers diagnosed before the mid-1990s. For this study, only adults aged 20-79 years were included.

Mortality data

Thyroid cancer deaths by sex and 5-year age groups occurring between 1/1/1973 and 12/31/2011 were obtained from SEER data using data provided by the National Center for Health Statistics. These data include all deaths within the United States, not just the nine SEER cancer registry areas. Population data from the United States Census data for the whole country were also obtained from the SEER data. As with the incidence data, only those aged 20-79 years were included.
2.2.2. Measures


The histological subtypes included were papillary carcinoma (ICD-O-3 histology codes 8050, 8260, 8340-8341, 8343-8344, and 8350), follicular carcinoma (ICD-O-3 histology codes 8290, 8330-8332, and 8335), medullary carcinoma (ICD-O-3 histology codes 8345-8346 and 8510), and anaplastic carcinoma (ICD-O-3 histology codes 8012, 8020-8021, and 8030-8032). All other ICD-O-3 histology codes were categorized as other/unknown and while included in the primary analyses, were excluded from the secondary analysis.

2.2.3. Statistical Analysis

Age-adjusted incidence and mortality rates and 95% confidence intervals were calculated using the SEER*stat program (Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.1.5) and were standardized to the 2000 United States standard population.

For the primary analyses including all thyroid cancers cases, Poisson regression models corrected for over-dispersion were fit to the population estimates for the respective age group, calendar period and birth cohort serving as the denominator in an offset term. The full age-
period-cohort model used to estimate the rate of thyroid cancers \((Y_{ij})\) for age group \(i\) in calendar period \(j\) was the following:

\[
Y_{ij} = \log(n_{ij}) + \alpha_i + \beta_j + \gamma_k + \epsilon_{ij}
\]

Where \(\alpha, \beta, \) and \(\gamma\) represent the age groups, calendar periods and birth cohorts, respectively for the age effect \((\alpha_i)\), the period effect \((\beta_j)\) and the cohort effect \((\gamma_k)\) and where \(n_{ij}\) denotes the total population for age group \(i\) and calendar period \(j\). In addition to the full age-period-cohort model, the following models were fit: age effect only, age and drift effects, age and calendar period effects, and age and birth cohort effects. The drift effect, included in the model as a continuous measure, assesses the linear change over time, while the period and cohort effects assess the non-linear change. To correct for over-dispersion, standard errors, confidence intervals, and P-values were adjusted using Pearson’s chi-square statistic divided by the number of degrees of freedom in the model.

When assessing age, period, and cohort effects in the full model, it is impossible to identify each effect separately because the age, period and cohort variables are related to each other. To overcome this non-identifiablity problem, constraints were assigned to equate the second and penultimate periods. The age group 50-54 years, the time periods 1978-1982 and 2003-2007 and the birth cohort 1903 were used as the reference groups for the full age-period-cohort models. The estimates from the age-period-cohort models were plotted to visually identify the turning points (also known as inflection points) for the effect. Akaike’s information criterion (AIC) was used to determine the goodness of fit for each model, with the lowest values representing the best fitting model. Because age-adjusted thyroid cancer rates differ by sex, we assessed whether age,
calendar or birth cohort effects differed by sex from model fit with and without the relevant
interaction terms, and sex-stratified analysis was presented where differences by sex existed.

Four secondary analyses were conducted. First, the primary analyses were repeated separately by
race for whites and blacks (ethnicity was not available in the SEER 9 data so Hispanic ethnicity
could not be included). Second, the analyses were conducted separately for histological subtypes
of thyroid cancer. The histological subtypes included were papillary carcinoma, follicular
carcinoma, medullary carcinoma, and anaplastic carcinoma. Next, the third analysis was to
assess the influence of early detection by improvements in medical procedures as smaller tumors
would be diagnosed as a result. The primary analyses were repeated for non-palpable tumors (<2
cm) and palpable tumors (2 cm or greater). Tumors measuring larger than 20 cm were
considered errors and were not included in the large category. The third analyses were
restricted to the time period between 1988 and 2011 because the size of the tumor was only
available during this time. Finally, using national cause of death data the age-period-cohort
analyses were conducted to decompose trends in mortality. For all secondary analyses, whether
age, period, or cohort effects varied by race, histological subtype, or tumor size, depending on
the secondary analysis, was assessed by examining model fit for models with and without the
relevant interaction terms. Stratified models are only presented where such differences were
evident.

As a sensitivity analysis, results from full age-period-cohort models for the primary outcome
using different reference groups for age, period and cohort were assessed.
All models were analyzed in the statistical software SAS (version 9.4; SAS Institute Inc., Cary, N.C., USA). The institutional review board for the City University of New York, New York, NY approved this study.

2.3. Results

The total number of thyroid cancers diagnosed during the study period within the nine geographic regions in the analyses was 66,359 (49,678 among women and 16,681 among men). Eighty-two percent of the cases were among whites (n=54,535), which is slightly higher than the population proportion of whites in the nine geographic regions (80%). Additionally, 83% of all thyroid cancers were papillary carcinoma tumors (n=55,197). The median age of diagnosis during the last five years of the study was 50 years and was slightly higher than the median age during the first 5 years, 45 years. Thyroid cancer incidence increased with calendar period, with rates among women being greater than among men for the whole study period. As seen in Figure 2.1, the age-adjusted incidence rate among women increased faster than among men during the study period while the age-adjusted mortality rate remained unchanged for men and women. In race-specific analyses, the age-adjusted incidence rates increased for both whites and blacks (Figure 2.2) but when examined by subtype, the increase over time was primarily among papillary tumors (Figure 2.3). In terms of tumor size, the age-adjusted rate for both non-palpable (<2 cm) and palpable (≥2 cm) tumors increased during follow-up, but the rate for non-palpable tumors among women increased slightly faster (Figure 2.4).
2.3.1. Age-Period-Cohort Models

Displayed in Figures 2.5a and 2.5b are the age-specific incidence rates by calendar period for all thyroid cancer by sex and Figures 2.5c and 2.5d show the age-specific incidence rates by birth cohort for all thyroid cancer by sex. While easier to see among the women, the age-specific rates increased during the last three calendar periods for both men and women. The age-specific rates also increased for those born after the 1920s.

The models with an interaction term between sex and age group, calendar period and birth cohort fit better than the models without the interaction term (data not shown) and therefore, all analyses were stratified by sex. For the primary analysis, a full age-period-cohort model fit best for both women and men (Table 2.1). Each model showed downward turning points in the late 20s age groups, upward turning points in the period 1993-1997 and upward turning points for the birth cohort born in the early 20th century and then a downwards turning point for the early 1970s birth cohort (Figures 2.6a and 2.6b). Results from the sensitivity analysis using different reference points showed turning points that were similar. The age-adjusted rates for women and men prior to the turning point in 1993 were 9.4 per 100,000 persons (95% CI 9.2-9.6) and 3.9 per 100,000 (95% CI 3.8-4.0), respectively and after 1997 the rates were 22.4 per 100,000 (95% CI 22.1-22.6) and 7.5 per 100,000 (95% CI 7.3-7.6), respectively.

For the secondary analyses, in addition to the interaction with sex, models with interaction terms between age group, calendar period and birth cohort and either race, subtype of thyroid cancer, or size of the tumor depending on the specific secondary analyses, improved the fit of the models so the analyses were stratified by sex and either race, subtype of thyroid cancer or size of the
tumor (data not shown). Results for the secondary analyses showed the full age-period-cohort model fit best for only some of the outcomes (Table 2.1).

The effects from the full age-period-cohort models for each of the secondary analyses are displayed in Figures 2.6a and 2.6b. Among analyses that were restricted to whites, the full age-period-cohort model fit best for women and men and showed similar turning points as were observed in the primary analyses. While the full age-period-cohort models were not the best fitting models among analyses that were restricted to blacks, the turning points were mostly the same as those in the primary analyses with the exception of the turning points for the cohort effects, which did not show a turning point for those born in the early 1900s.

The best fitting models among all races differed by subtype. For both women and men, the full age-period-cohort model fit best for the papillary carcinoma subtype and the turning points were similar to those for all thyroid cancer, i.e., turning points were observed for the late 20s age group, the 1993-1997 period and the 1920s and 1970s birth cohorts (Figure 2.6a and 2.6b). Among the follicular carcinoma subtype the turning points for age and calendar period were also similar to the primary analyses but a downward birth cohort turning point in the second half of the 20th century was less clear. The age-period-cohort models for the medullary carcinoma and anaplastic carcinoma subtypes, while not the best fitting model for either outcome, showed slightly different turning points than the ones observed for all thyroid cancer. Among both women and men a turning point for the period effect was less clear for medullary carcinomas. A possible upward turning point in the late 1980s for the period effect was observed for anaplastic carcinomas among both women and men.
While the time period for analyses involving the size of the tumor was 15 years shorter than the primary analyses, the age-period-cohort models for non-palpable tumors (>2 cm) showed similar turning points to the primary analyses for the age and birth cohort effect (Figures 2.6a and 2.6b). An upward turning point began during the 1993-1997 period for women and men and an additional downward turning point during the 2003-2007 period for both is also possible. Analyses for palpable tumors (≥2 cm) were similar to the age-period-cohort models for non-palpable tumors.

Finally, in the age-period-cohort models for thyroid cancer mortality a slight upward turning point in the 1990s was observed for women and men. Additionally, an upward turning point for those born in the 1980s is possible however the rates are unstable during this time (Figures 2.6a and 2.6b).

2.4. Discussion

In an analysis of thyroid cancer incidence from 1973 to 2011, based on visual inspection we found an apparent upward turning point during the period of 1993-1997, suggesting a period influence affecting the population, one that is plausibly consistent with a hypothesis of increased medical detection due to the growth in CT scans and ultrasounds. In contrast, a turning point in the 1993-1997 period was not evident for an aggressive subtype of thyroid cancer, anaplastic carcinoma, more likely to be diagnosed in symptomatic patients than to be detected incidentally during a CT scan or ultrasound. We also found a turning point round the late 20s age group and turning points for those born around the 1920s and 1970s.
Using age-period-cohort methods Zheng et al investigated thyroid cancer incidence in Connecticut between 1935 and 1992 and concluded the increase was mainly due to a birth cohort effect among those born between 1910 and 1945 after which the rate of thyroid cancer decreased.\textsuperscript{45} The authors suggested those born during the first half of the 20\textsuperscript{th} century experienced an increase risk of thyroid cancer as a result of childhood radiation treatment for benign conditions. We also found a similar effect for those born in the early 20th century but the upward turning point began about a decade later and we did not observe a downward turning point until the 1970s, about 10 to 20 years after the radiation treatments for benign childhood conditions were discouraged in the United States.\textsuperscript{45,55,56} Kilfoy et al and Zhu et al both used age-period-cohort analyses to describe thyroid cancer incidence in the United States from 1976 to 2005.\textsuperscript{46,47} Kilfoy et al only assessed incidence of papillary tumors using age-period-cohort analyses with a drift estimate. They found the secular trend in incidence differed by gender but did not investigate separate period and cohort effects.\textsuperscript{47} While Zhu et al also did not analyze a period effect, they did find the risk of thyroid cancer in the United States decreased for those born after the 1970s but did not postulate reasons for this change.\textsuperscript{46} The authors suggested radiation exposure from X-rays could be related to the increasing incidence rate nationally,\textsuperscript{46} however by fixing the period effect their analyses could not formally test this. If this was true, a similar pattern would be expected for leukemia incidence, a cancer caused by radiation,\textsuperscript{16} but incidence rates for leukemia have remained mostly stable since the 1970s.\textsuperscript{1} Additionally, to date, studies examining the association between low dose radiation exposure from X-rays and risk of thyroid cancer suggest the magnitude of the relative association is close to one, if present at all.\textsuperscript{57-60} Furthermore, based on the latency of at least four years between radiation exposure from
disasters, such as Chernobyl, and thyroid cancer, we would expect the observed period effect in the current study to occur several years after the early 1990s when the use of diagnostic procedures involving radiation began to increase instead of at the same time. As a result, we do not believe radiation exposure from these procedures is the main reason for the increase in thyroid cancer.

In addition to radiation exposure from either CT scanners or X-rays, there are several possible explanations for the increase in thyroid cancer largely driven by a period effect, albeit with a contribution from age and cohort effects. For example obesity and smoking have been implicated as possible risk factors for thyroid cancer. While obesity could contribute to the rates, the national trend in obesity does not explain the period effect we observed because the prevalence of obesity was highest in the 1980s. Additionally, it has been suggested that those born during the second half of the 20th century have a higher prevalence of obesity; this would not explain the downward turning point we observed in the 1970s birth cohort. Similarly, changes in cigarette smoking do not explain the observed turning points. Smoking has been suggested to protect against thyroid cancer so among the birth cohorts with the lowest smoking rates, those in the late 20th century, thyroid cancer rates would be expected to increase. We did not show this to be true.

Further, national changes in TSH levels and iodine deficiency could explain the increase in thyroid cancer however it is unlikely. TSH levels have decreased since the late 1980s, and if higher levels are associated with thyroid cancer, this does not explain the observed period effect. Also, the prevalence of iodine deficiency has increased slightly in the United States since...
the 1970s and has since leveled off. It is possible that this increase is related to the observed period effect; however because iodine deficiency is thought to increase the risk of follicular tumors, a period effect among follicular tumors, rather than papillary tumors, would be expected.

Taking all the evidence together, the most likely reason for the observed period effect is the incidental detection of asymptomatic cancers. Medical diagnostic procedures began to increase in the 1980s but they increased dramatically during the early 2000s. For example, a study in United States health care groups reported a three-fold increase in CT use between 1996 and 2010 to an annual rate of 149 per 1,000 persons, and the rate also increased with age. During this time, through improvements in medical technology, it has become easier to detect abnormalities as small as 2 to 3 mm. For women the rate of thyroid cancer increases during the reproductive years, a period when women receive more medical attention than men and therefore, are more likely to receive more diagnostic procedures. This would explain the more pronounced increases observed in age-adjusted (Figure 2.1) and age-specific (Figure 2.5) incidence among women compared to men since the 1990s. The time of the increase in the rate of diagnostic procedures parallels the calendar period turning point we observed in thyroid cancer incidence. This simultaneous increase in rates, particularly during ages when women and men are more likely to receive medical attention for other reasons, suggests the thyroid cancers are possibility being incidentally detected during unrelated procedures and further supports a similar conclusion from Morris et al. Thus, it is possible that this is the reason for the rising incidence rate nationally and in countries with similar diagnostic procedures available, such as Italy, Korea and Canada.
We also found that while the rate of non-palpable tumors (<2 cm) increased during the follow-up period, the rate of larger tumors (≥2 cm) also increased; others have observed this as well. This argues that incidental detection from increased medical attention may not be the only factor causing the increase in thyroid cancer incidence because earlier detection would lead to smaller tumors. However, based on autopsy findings, it is possible that the prevalence of larger asymptomatic tumors that have yet to be diagnosed remains high, and as more of these larger tumors are detected incidentally, the incidence will decrease over time as the pool of larger tumors is depleted.

The analyses of thyroid cancer mortality showed there was an upward turning point during the 1990s but the mortality rate remained very low at all time periods throughout the study (about 0.5 per 100,000). While this turning point coincides with the time of increased use of diagnostic procedures, it is possible that those who died during this period died of complications due to treatment or were diagnosed with thyroid cancer many years before since the 5-year survival rate thyroid cancer is high. More follow-up time may be needed to fully understand this relationship and whether a lag between diagnosis and death is influencing the observed turning point in thyroid cancer mortality rates.

Unfortunately, case history was not available for this study and we do not know how the cases were diagnosed or if the persons were symptomatic at the time. This is the main limitation of the study, because without this information we cannot draw causal associations between the use of diagnostic procedures and the thyroid cancer diagnoses. Additionally, in order to maximize the
amount of follow-up time for the study, we used cancer data from the SEER 9 registries, which only represents about 9% of the United States population. It is possible that finding from this study may not be fully generalizable to the entire United States population, however there is no reason to think that secular trends in use of diagnostic procedures such as CT scans is different for places covered by SEER 9 and elsewhere, or that the relation between diagnostic procedures and thyroid cancer is different in the SEER 9 areas than elsewhere. Another limitation is that these analyses are descriptive and the observed turning points may not be statistically significant. Future studies may consider methods such as change point regression\textsuperscript{73,74} to determine significant turning points. Nonetheless, these analyses are consistent with the hypothesis that incidental detection is influencing the trend in thyroid cancer and are informative for future studies. The main strengths of this 39-year study are that it provides the longest period of examination of thyroid cancer trends in the United States\textsuperscript{12} and includes time periods both before and after the national increase in use of CT scans and ultrasounds. Additionally, for the age-period-cohort analyses we used the Holford method of applying constraints to overcome the non-identifiability issue. This method is considered to produce reliable estimates,\textsuperscript{75} unlike the intrinsic estimate method, which can lead to different conclusions depending on chosen exclusions.\textsuperscript{76} Further analyses of thyroid cancer incidence could be strengthened by also including the curvature estimates to help identify clear and unbiased turning points.\textsuperscript{52,75}

Our findings suggest that the rate of incidental thyroid cancers are likely to continue increasing, regardless of tumor size, as the ability for medical detection of tumors continues to improve. The standard treatment for thyroid cancer is a total thyroidectomy and in many cases radioactive iodine ablation.\textsuperscript{54,77} In the United States this course of treatment has been applied to about three
quarters of the papillary thyroid cancers smaller than 1cm in size.\textsuperscript{3,78} It is not yet known if aggressive treatment such as total thyroidectomy is necessary for thyroid cancers of this size which were most likely detected by increased sensitivity of medical technologies.\textsuperscript{78} Further, it is possible that these aggressive treatments may expose patients to additional risks, such as complications from surgery.\textsuperscript{72} Consequently, it is important that the best course of treatment for these thyroid cancers, which may include no treatment, is determined after weighing all the risks and benefits.\textsuperscript{78}

The findings from this nearly four-decade long study demonstrate a greater rate of thyroid cancer beginning in the 1990s, which may be a result of increased detection of asymptomatic tumors during medical procedures conducted during the same time. The increase in incidence rate was observed for both men and women but was greater for women, possibly due increased medical attention. To fully understand the impact of detection of incidental tumors on the increased rate of thyroid cancer, studies with longer follow-up to assess if the tumor size patterns diverge and any possible effects on mortality are needed, as are studies with more detailed information regarding the history of case diagnosis, to help determine a causal relationship.
Table 2.1 Akaike’s Information Criterion (AIC) Values for Age, Age-Drift, Age-Period, Age-Cohort, and Age-Period-Cohort Models Assessing Risk of Thyroid Cancer in the United States from 1973-2011 by Sex

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women</th>
<th>AIC Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Cases</td>
<td>Age Model</td>
</tr>
<tr>
<td>All Thyroid Cancers</td>
<td>49,678</td>
<td>10,818</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40,364</td>
<td>10,190</td>
</tr>
<tr>
<td>Black</td>
<td>3,135</td>
<td>1,161</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>42,135</td>
<td>12,030</td>
</tr>
<tr>
<td>Follicular</td>
<td>5,273</td>
<td>763</td>
</tr>
<tr>
<td>Medullary</td>
<td>896</td>
<td>544</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>397</td>
<td>330</td>
</tr>
<tr>
<td>Size of Tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>22,794</td>
<td>6,075</td>
</tr>
<tr>
<td>2+ cm</td>
<td>13,722</td>
<td>1,685</td>
</tr>
<tr>
<td>Thyroid Cancer Mortality*</td>
<td>18,526</td>
<td>933</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Thyroid Cancers</td>
<td>16,681</td>
<td>2,802</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>14,171</td>
<td>2,864</td>
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<tr>
<td>Black</td>
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<tr>
<td>Subtype</td>
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</tr>
<tr>
<td>Papillary</td>
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<td>3,094</td>
</tr>
<tr>
<td>Follicular</td>
<td>2,158</td>
<td>608</td>
</tr>
<tr>
<td>Medullary</td>
<td>600</td>
<td>454</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>305</td>
<td>322</td>
</tr>
<tr>
<td>Size of Tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>5,585</td>
<td>1,605</td>
</tr>
<tr>
<td>2+ cm</td>
<td>5,796</td>
<td>929</td>
</tr>
<tr>
<td>Thyroid Cancer Mortality*</td>
<td>14,278</td>
<td>814</td>
</tr>
</tbody>
</table>
Note: For nested models the models with lower AIC values fit better. The best fitting model for each outcome is shown in bold font.
*United States cause of death data includes all deaths in the United States. Data are not restricted to the nine Surveillance, Epidemiology and End Results regions from which the incidence data are obtained.
Figure 2.1 Age-Adjusted Incidence and Mortality Rates for Thyroid Cancer among Men and Women Aged 20-80 in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.2 Age-Adjusted Incidence Rates for Thyroid Cancer by Race among Men and Women Aged 20-80 in the United States from 1973 to 2011

Note: rates are for all types of thyroid cancer.
Figure 2.3 Age-Adjusted Incidence Rates for Thyroid Cancer by Type of Thyroid Cancer among Men and Women Aged 20-80 in the United States from 1973 to 2011

Note: rates are among all race groups.
Figure 2.4 Age-Adjusted Incidence Rates for Thyroid Cancer by Tumor Size among Men and Women Aged 20-80 in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.5a Age Specific Thyroid Cancer Incidence Rates by Calendar Period for Women in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.5b Age Specific Thyroid Cancer Incidence Rates by Calendar Period for Men in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.5c Age Specific Thyroid Cancer Incidence Rates by Birth Cohort for Women in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.5d Age Specific Thyroid Cancer Incidence Rates by Calendar Period for Men in the United States from 1973 to 2011

Note: rates are among all race groups and for all types of thyroid cancer.
Figure 2.6a Parameter Estimates for Age, Period and Cohort Effects in Thyroid Cancer Incidence and Mortality for Women in the United States from 1973 to 2011, by Race, Type of Cancer and Tumor Size and Overall for Mortality.
Age - Tumor Size: >2cm

Period - Tumor Size: >2cm

Birth Cohort - Tumor Size: >2cm

Age - Mortality

Period - Mortality

Birth Cohort - Mortality
Figure 2.6b Parameter Estimates for Age, Period and Cohort Effects in Thyroid Cancer Incidence and Mortality for Men in the United States from 1973 to 2011, by Race, Type of Cancer and Tumor Size and Overall for Mortality.
Chapter 3: Exposure to Radiation from Diagnostic Procedures and Risk of Thyroid Cancer in New York City Firefighters

3.1. Introduction

Thyroid cancer is currently among the 15 most commonly diagnosed cancers in the United States with an incidence rate of 19.1 per 100,000 among women and 6.4 per 100,000 among men. In 2011, the Fire Department of the City of New York (FDNY) reported the incidence of thyroid cancer among World Trade Center (WTC)-exposed firefighters to be more than twice the overall rate among men in the United States, adjusting for age and race/ethnicity. While exposure assessment studies of dust at the WTC disaster site did identify some carcinogens such as asbestos and polycyclic aromatic hydrocarbons, to date, none has been directly linked to thyroid cancer. Currently, the risk of thyroid cancer after occupational exposures from firefighting has not been well established and no clear, plausible causal mechanism for the observed rate of thyroid cancer among FDNY firefighters has been articulated. The most widely recognized causal factor for thyroid cancer is exposure to ionizing radiation; most fire settings do not have elevated levels of ionizing radiation, nor were levels reported to be high at the WTC site after the disaster. One longitudinal study among a cohort of Florida firefighters documented a higher risk of thyroid cancer than the general population of Florida, but this finding was not replicated in other observational studies using both case-control and cohort designs, and a meta analysis also did not find higher risk. FDNY and many firefighters in the United States are, however, routinely exposed to low levels of ionizing radiation during medical diagnostic procedures (such as chest X-rays) approximately biennially throughout their career, which is more than non-firefighters typically experience.
Exposure to ionizing radiation can occur during nuclear disasters, medical treatments for cancer and some benign conditions, and medical diagnostic procedures. Exposure to high dose of radiation has consistently been found to be associated with the development of thyroid cancer, most notably from the World War II atomic bombings, the Chernobyl disaster, and from medical treatments for cancer and benign conditions, particularly among children. Radiation exposure from medical diagnostic procedures, however, can be a small fraction of the dose experienced during nuclear disasters and medical treatments; the average effective dose from diagnostic procedures is below 10 mSv (or 1000 milliRem) and in many cases, such as X-rays, it is less than 1 mSv. To date, only a limited number of studies have investigated the association between exposure to radiation from medical diagnostic procedures and thyroid cancer, and the results have been inconclusive, particularly in regards to exposure during adulthood. The majority of these studies investigated the association between radiation exposure from X-rays and thyroid cancer. Two case-control studies have shown significantly higher odds of thyroid cancer among individuals with at least one X-ray as adults compared with those without an X-ray (odds ratios [OR] ranging from 1.80 to 5.40), but exposure was self-reported in these studies. Others, two of which used medical records to define X-ray exposure, reported non-significant but elevated risks of thyroid cancer following exposure multiple X-rays (ORs ranging from 1.02 to 1.40). Only one recent study has investigated the association between diagnostic or screening computerized tomography (CT) scan procedures and the development of thyroid cancer and this study was only among those exposed during childhood. This retrospective cohort study followed nearly 11 million individuals from the Australian national healthcare system beginning in childhood, with many followed for up to 22 years. Using medical records to estimate exposure to CT scans, the investigators of this study found a 40% higher risk of thyroid cancer
among participants exposed to CT scans during childhood compared with those not exposed (hazard ratio [HR]=1.40; 95% CI 1.23-1.59). To date, no meta-analyses have been conducted regarding the association between radiation exposure from diagnostic procedures and thyroid cancer.

Other potential causes of thyroid cancer such as obesity and differences in thyroid stimulating hormone have been investigated, but none are yet well established. Some recent studies have suggested that smoking is associated with a lower risk of thyroid cancer however, others have found no association. Additionally, some studies have suggested greater access to healthcare, such as through Medicare or high socioeconomic status is associated with a higher rate of thyroid cancer diagnoses.

Given that the risk of thyroid cancer following high doses of radiation exposure in children and adults has been well documented, it would be expected that low doses of radiation could also have lower, but none-null, risks. However, the association between exposure to radiation from diagnostic procedures and thyroid cancer, particularly among adults, has not yet been clearly demonstrated, often due to a lack of well-defined and objective measures of X-ray or CT scan exposure. Understanding the cancer-related risks associated with commonly used diagnostic procedures involving ionizing radiation is an understudied public health issue. The aim of this study was to estimate the association between exposure to radiation from diagnostic procedures and risk of thyroid cancer development among a highly exposed adult population, the FDNY firefighters.
3.2. Methods

3.2.1. Study Population

The study cohort was drawn from the population of FDNY firefighters who were active on 9/11/2001 as well as those hired between 9/11/2001 and the end of the study, 12/31/2013 (n=16,454). Firefighters who retired prior to the start of the study were excluded because some FDNY medical records were incomplete prior to 9/11/2001. Additionally, 137 firefighters with a history of cancer before the start of follow-up were excluded because treatment for cancer, such as radiation therapy, may increase the risk of a subsequent cancer.\textsuperscript{8,50} Non-white firefighters were excluded due to small numbers and well-documented differences in incidence rates in the United States (n=1,552).\textsuperscript{1} Lastly, due to small numbers females (n=41) were excluded, resulting in the final study population of 14,724 non-Hispanic white, male firefighters.

3.2.2. Exposure

The main exposure in this study was radiation from diagnostic procedures. Through the FDNY Bureau of Health Services, active and retired firefighters receive monitoring exams about every 12-18 months and, if needed, separate treatment exams. Treatment exams occur either by physician referral or self-referral. During the monitoring exams chest X-rays were conducted approximately biennially. Chest CT scans, sinus CT scans, and PET scans were also conducted by FDNY among symptomatic patients when clinically needed. Additionally, firefighters who were present at the WTC disaster site on 9/11/2001 or were smokers were offered a chest CT scan as part of a screening program. The number and types of diagnostic procedure firefighters received during the study period was obtained from the FDNY medical records which contain information on procedures conducted or paid for by FDNY. Because diagnostic procedures can
lead directly to a diagnosis of cancer, the date of all diagnostic procedures was lagged by one year to reduce the possibility that thyroid cancers detected incidentally during these procedures would be included in the analysis and bias the association of interest.\textsuperscript{33} A total of 7,923 procedures (17 PET scans, 423 sinus CT scans, 788 chest CT scans, and 6,695 chest X-rays) were excluded as a result of this lag because the lagged procedure date was after the end of follow-up for the individual.

Individual exposure to radiation was not measured for participants in the study population; therefore, the effective dose was estimated using published national average radiation doses for each type of diagnostic procedure,\textsuperscript{22,23,51-55} and information from the radiology department at New York University where most chest CT scans (more than 75\%) were conducted (Table 3.1).\textsuperscript{56,57} The influence of radiation exposure was first examined as a continuous variable then as a categorical variable to assess for possible nonlinear effects. The categorical variable was initially constructed with four levels to reflect estimated exposure levels associated with different types and frequencies of diagnostic procedures: 0-2.4 mSv (equivalent to less than a low dose chest CT scan), 2.5 mSv-5.0 mSv (equivalent to one low dose chest CT scan), 5.1 mSv-10.0 mSv (equivalent to one chest CT scan) and ≥10.1 mSv (equivalent to more than one chest CT scan).\textsuperscript{22} The first two groups, 0-2.4 mSv and 2.5 mSv-5.0 mSv, were combined as the reference group in the analyses because less than 1\% of the observations were in the 2.5 mSv-5.0 mSv group (n=143).

3.2.3. Outcome
FDNY maintains an internal cancer registry, which acquires information on cancer cases among active and retired FDNY firefighters from two sources. First, the largest source of cases comes from matches to nine state cancer registries including New York, Florida, Pennsylvania, North Carolina, Virginia, New Jersey, Connecticut, South Carolina, and Arizona, states selected for being places where the greatest proportion of firefighters move after retirement. Second, cancer cases were also self-reported on self-administered questionnaires during the monitoring exams or reported to a FDNY physician during a medical evaluation, and therefore captured in the electronic medical record. A trained clinician contacts all participants who reported a cancer not already received during matches to state cancer registries and requests documentation. As with cases from state cancer registries, FDNY confirmation required a pathology report or detailed treating physician notes/evaluations (operative reports, oncology notes with diagnosis/treatment, formal consultations from related specialists, and/or physical findings consistent with oncologic treatments/modalities). Malignant thyroid cancer cases (ICD-O-3 site code C739) diagnosed during follow-up from either a state cancer registry source or confirmed by FDNY were included as the outcome of interest.

3.2.4. Potential Confounders

Age on 9/11/2001 and WTC exposure on 9/11/2001 were considered potential confounders based on the literature. Additionally, due to sparse, and at times inconclusive, evidence of an association with thyroid cancer in the literature, we explored to see if smoking status and number of medical exams received during the study period were confounders in this FDNY firefighter population. Firefighters present at the WTC disaster site on 9/11/2001 or who were smokers were offered CT scans though FDNY, in many cases without clinically indicated symptoms. The
remaining firefighters were provided CT scans if clinically indicated.\textsuperscript{58} As mentioned above, increased age and WTC exposure have been observed to be associated with a higher risk of thyroid cancer.\textsuperscript{2,59,60} In contrast, cigarette smoking may be associated with a lower risk of thyroid cancer.\textsuperscript{43-45} The frequency of medical exams may have influenced the number of medical diagnostic procedures a firefighter received and as a result increased exposure to radiation and the frequency of exams could also possibly increase the likelihood of detecting thyroid cancer.

Demographic data including age on 9/11/2001 were obtained from the FDNY employee database. The self-administered health questionnaires, which began in 2001, were administered on computers during the monitoring exams and data were also recorded electronically. Self-reported WTC exposure and smoking status were obtained from the questionnaires. For this study WTC exposure was defined as being present at the WTC disaster site on 9/11/2001 or not. Participants missing WTC exposure information were classified as being not present at the WTC disaster site (n=190). Smoking status was defined as ever if the participant answered positively to being a current or former smoker on any of the questionnaires. If a participant consistently answered never smoking, he was defined as a never smoker. Additionally, 201 participants who were missing information regarding smoking status were included as never smokers. Medical monitoring exams are required every 12 to 18 months; during follow-up the mean number of monitoring exams per person was eight. The total number of medical exams, either monitoring or treatment, was categorized as having up to the average number exams (≤8 exams) or for those with more than eight exams, the number of medical exams were grouped into quartiles (9-28 exams, 29-45 exams, 46-67 exams and ≥68 exams).
3.2.5. Statistical Analysis

Person-time at risk began on 9/11/2001 or date of hire if later. Among participants who were active firefighters at the end of the study, 12/31/2013, follow-up ended on earliest date of either the first cancer diagnosis (thyroid or other cancer) or 12/31/2013. Follow-up was censored for all participants at the diagnosis of any cancer because some cancer treatments may increase the risk of thyroid cancer.\textsuperscript{8,50} For participants who retired during the study period, regardless of state of residence, follow-up ended on earliest date of the following events: first cancer diagnosis (thyroid or other cancer), the last date of contact, or 12/31/2013; the last date of contact was defined as either the retirement date or the last medical exam, depending on which occurred last. Retired firefighters without a current medical exam, within the two years prior to the end of the study, were considered lost to follow-up (n=1,247, 8\%) and were censored at the last date of contact. Differences in baseline characteristics between those lost to follow-up and those who remained in the study were assessed using the Pearson chi-square test and Student’s t-test, for categorical and continuous variables, respectively.

Cox models were fit with cumulative exposure to radiation included as a time-dependent variable, with calendar time since 9/11/2001 as the underlying time variable. For analyses using a continuous level of radiation, exposure increased by the specified amount depending on the particular diagnostic procedure one year after the date of the procedure to account for the lag (Table 3.1). Similarly, for secondary analyses using categories of radiation, the variable increased to the next radiation exposure category one year after the date of the procedure, which caused the cumulative exposure dose to correspond to that level. Potential confounders (age on 9/11/2001, and WTC exposure) were included in the final multivariable models. Smoking status
and number of medical exams were explored as potential confounders in this dataset using univariable analyses to determine whether they should be included in multivariable models as sensitivity analyses based on an observed associations with both radiation exposure and thyroid cancer. Hazard ratios and corresponding 95% confidence intervals (95% CI) were calculated from the models. P-values less than 0.05 were considered statistically significant.

A sensitivity analysis was conducted using different radiation dose levels per diagnostic procedure to assess the impact of the dose level chosen on main study findings. Because the radiation dose for each procedure can vary within a given range that is commonly referenced in radiation literature, the exposure variable for the sensitivity analysis was defined by the upper bound of the range, rather than the most referenced dose which was used for the main analysis. These values are shown in Table 3.1. A second sensitivity analyses was conducted to evaluate the influence of those lost to follow-up. This analysis restricted the study population to participants who were active on 9/11/2001 (n=10,164) because the majority of those lost to follow-up were active on 9/11/2001 (87%).

Based on the sample size and the number of thyroid cancer cases, it was expected that we would have 80% power to detect a HR between 1.62 and 2.14 for a one standard deviation increase in radiation exposure depending on the level of correlation with other variables in the model (Table 3.2).

All analyses were performed using the statistical software SAS (version 9.4; SAS Institute Inc., Cary, N.C., USA). The institutional review boards for The Albert Einstein College of Medicine
and Montefiore Medical Center, Bronx, NY; and for the City University of New York, New York, NY approved this study.

3.3. Results
The study population characteristics are shown in Table 3.3. During the course of the 12-year study, the average person-time at risk was 10.5 years. The average age on 9/11/2001 was 35 years and 63% of the cohort (n=9,343) never smoked by end of follow-up. By the end of the study, 5,927 participants (40%) had retired from FDNY and the average radiation exposure from diagnostic procedures among firefighters was 2.36 mSv (SD 4.77), with 8% of the cohort exposed to 10 mSv or greater (Table 3.3). A total of 33 cases of thyroid cancer were diagnosed during follow-up. Those lost-to-follow-up (n=1,247) were similar to the remaining study population on most characteristics, with the exception that they were significantly older on 9/11/2001 (41 years verses 35 years), more likely to be active firefighters on 9/11/2001 (87% verses 67%), and were documented as being exposed to slightly less cumulative radiation by the end of their follow-up (1.61 mSv verses 2.44 mSv).

Participants with the highest level of radiation exposure by the end of follow-up were on average older than those with lower levels of exposure (Table 3.4), and those who were present at the WTC site on 9/11/2001 had higher levels of radiation exposure than those who were not present on 9/11/2001. The majority of participants with thyroid cancer (81.8%) were exposed low levels of radiation from diagnostic procedures (<2.5 mSv).

3.3.1. Main Analyses
The unadjusted association between radiation exposure from diagnostic procedures and thyroid cancer was not statistically significant for both the continuous measure (Table 3.5) and the
secondary categorical measure (Tables 3.6). Smoking status and number of medical exams were not associated with a diagnosis of thyroid cancer in this population and therefore, were not included in the final models (Appendix Table 3.5). Age on 9/11/2001 and WTC exposure were included in the final models; however, neither variable remained statistically significant. While not statistically significant, the largest association after adjusting for age and WTC exposure was among those with radiation exposure of 10.1 mSv or greater (HR=1.91, 95% CI 0.55-5.18) (Table 3.6). Additionally, no association was found when the two exposure groups, 5.1 to 10.0 mSv and 10.1 mSv or greater, were combined (HR=1.35, 95% CI 0.49-3.30). By the end of follow-up the mean cumulative dose for those in the highest exposure group was 9.79 mSv (SD 6.18).

3.3.2. Sensitivity Analyses

Results from the first sensitivity analyses using the upper bounds of the estimated dose range are shown in Table 3.6. The association between radiation exposure from diagnostic procedures and thyroid cancer remained not statistically significant. Table 3.6 also shows the results from the second set of sensitivity analyses that restricted the analyses to participants who were active on 9/11/2001. The associations between radiation exposure from diagnostic procedures and thyroid cancer from these analyses were similar to the main analyses and were also not statistically significant.

3.4. Discussion

This study found exposure to radiation from diagnostic procedures was not associated with the risk of thyroid cancer among a population of over 14,000 male firefighters, but the observed risk
was positive and higher by 2% for every unit increase in mSv. However, the confidence interval included no association, suggesting that random error causing this observed modest increase in risk cannot be ruled out. Similarly in the categorical analysis among those with highest level of radiation exposure (10.1 mSv or greater) the risk of thyroid cancer was greater than among those with the lowest level of exposure (5.0 mSv or lower) but not statistically significant.

When the two levels of radiation exposure were combined (5.1 mSv or greater) the magnitude of the association, which was also not statistically significant, was similar in magnitude to the association observed among children exposed to at least one CT scan (HR=1.35 verses HR=1.40). However, the definition of radiation exposure differed between the studies; over 80% of the exposed population in the Mathews et al was exposed to only one CT scan and the average dose among the exposed was about 5.6 mSv. In the current study the level of exposure was greater (average total dose was 9.79 mSv) and therefore, it appears adult exposure to radiation from diagnostic procedures may not carry the same risk as childhood exposures. While a lower dose of radiation exposure, this is consistent with studies of adult exposure to X-rays that used medical records to define the exposure. Additionally, the results from the sensitivity analyses that used the upper bound of the exposure range showed no association between exposure to radiation from diagnostic procedures and thyroid cancer. This suggests the main analyses were less likely to be influenced by the assignment of the level of radiation dose.

Prior studies have shown an increased risk of thyroid cancer following exposure to the WTC disaster in this population and others. While in this study we investigated if the risk of thyroid cancer was a result of radiation exposure and found no association, we did observe that
WTC exposure and thyroid cancer were associated in an unadjusted model. This association is similar to the previous literature. Whether this association is due to a causal link between WTC exposures and thyroid cancer or due to increased surveillance is unknown. Chapter 4 will investigate if increased surveillance among those highly exposed to the WTC disaster mediated the observed association.

The current study has a number of strengths. The study population of 14,724 firefighters is a homogenous population with similar access to care, as well as potential occupational exposures. In addition, because the firefighters receive medical care through the FDNY, the date and type of diagnostic procedures could be assigned using medical records rather than self-report. Similarly, all cancer cases were confirmed by medical records or state cancer registry information, further reducing the potential of misclassification within the study. The time-dependent method used to analyze the association between exposure to radiation from diagnostic procedures and thyroid cancer allowed for the level of exposure to increase during the study period and therefore, risk of thyroid cancer was assessed based on the experienced exposure at that particular time. Additionally, while 8% of the cohort was lost to follow-up, we believe these individuals did not bias the results because the results from the second sensitivity analysis were similar to the main results. Lastly, the diagnostic procedures included in this study, particularly chest CT scans, may detect thyroid cancer incidentally. To control for this, we excluded all diagnostic procedures that occurred within one year prior to a diagnosis of cancer by lagging the procedure date by one year and therefore delaying the exposure until after the end of follow-up.
There are five main limitations to this study. First, radiation dose was not directly measured for this study and was estimated based on published national average radiation doses. The results from the sensitivity analysis using other radiation dose values were similar to the primary results and show the results were not likely to be biased by the selection of dose. Second, exposure to radiation from diagnostic procedures was limited to procedures conducted by FDNY and did not include exposures not included in the medical record. While untestable, it assumed that diagnostic procedures not conducted by FDNY did not differ by disease status and therefore, would equally underestimate any association between radiation exposure and thyroid cancer in this study. Third, for the continuous measure the study only had power to detect a hazard ratio of at least 1.62. Fourth, while it has been argued that thyroid cancer may have a short latency period, the study may have had insufficient duration to detect an association between radiation exposure and thyroid cancer. Lastly, the findings from this study are among a relatively healthy workforce of men and may not be generalizable to other populations.

In a population experiencing above-average exposure to radiation from diagnostic procedures, we did not observe a significantly higher risk of thyroid cancer after radiation exposure. Additional studies are needed to fully understand the relationship between diagnostic medical radiation exposure and thyroid cancer among adults and children.
Table 3.1: Assigned Dose per Type of Procedure in millisieverts (mSv) in the Primary Analyses and in the Sensitivity Analyses and the total number of procedure included in analyses

<table>
<thead>
<tr>
<th>Type of diagnostic procedure</th>
<th>Total number of procedures</th>
<th>Primary Analyses</th>
<th>Sensitivity Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-2005 Dose^a</td>
<td>Post-2005 Dose</td>
</tr>
<tr>
<td>First chest CT scan^b</td>
<td>3,004</td>
<td>10.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Follow-up Chest CT scan^47, 50,52,53,62</td>
<td>3,136</td>
<td>5.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Chest CT scan with contrast^c</td>
<td>59</td>
<td>10.0</td>
<td>5.0</td>
</tr>
<tr>
<td>PET scan^23</td>
<td>29</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Chest X-ray^33,47</td>
<td>49,362</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Sinus CT^23,51</td>
<td>2,106</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Sinus CT with contrast^c</td>
<td>19</td>
<td>1.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

^aEffective dose in mSv (1 mSv = 100 miliRem)

^bIncludes two scans for inspiratory and expiratory evaluations

^cCT scans with contrast include two scans, pre- and post-contrast scans^47
Table 3.2: Detectable hazard ratio (HR) for a one standard deviation increase in radiation exposure for power analysis

<table>
<thead>
<tr>
<th>Detectable HR</th>
<th>Correlation with other variables in model ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.62</td>
<td>0.0</td>
</tr>
<tr>
<td>1.71</td>
<td>0.2</td>
</tr>
<tr>
<td>1.86</td>
<td>0.4</td>
</tr>
<tr>
<td>2.14</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Table 3.3: Characteristics of study population of FDNY firefighters

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total white male firefighters</strong></td>
<td>14,724</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person years at risk</td>
<td></td>
<td></td>
<td>10.50</td>
<td>2.66</td>
</tr>
<tr>
<td><strong>Lost to follow-up</strong></td>
<td>1,247</td>
<td>8.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative exposure to radiation in mSv by end of follow-up</strong></td>
<td></td>
<td></td>
<td><strong>2.36</strong></td>
<td><strong>4.77</strong></td>
</tr>
<tr>
<td>(continuous measure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2.4 mSv</td>
<td>11,595</td>
<td>78.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mSv-5.0 mSv</td>
<td>36</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 mSv-10.0 mSv</td>
<td>1,908</td>
<td>12.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1 mSv or greater</td>
<td>1,185</td>
<td>8.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WTC exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>7,556</td>
<td>51.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>7,168</td>
<td>48.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age on 9/11/2001 (years)</strong></td>
<td></td>
<td></td>
<td>35.25</td>
<td>10.09</td>
</tr>
<tr>
<td><strong>Number of medical exams by end of follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8 exams</td>
<td>792</td>
<td>5.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-28 exams</td>
<td>3,605</td>
<td>24.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29-45 exams</td>
<td>3,524</td>
<td>23.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-67 exams</td>
<td>3,593</td>
<td>24.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 or greater exams</td>
<td>3,210</td>
<td>21.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status by end of follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>9,343</td>
<td>63.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>5,381</td>
<td>36.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active on 9/11/2001</strong></td>
<td>10,164</td>
<td>69.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retired during follow-up</strong></td>
<td>5,927</td>
<td>40.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis of thyroid cancer</strong></td>
<td>33</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Follow-up ended at the earliest of date of the following events: first cancer diagnosis (thyroid or other cancer), the last date of contact, or 12/31/2013.

Abbreviations:
FDNY = Fire Department of the City of New York
mSv = millisieverts
WTC=World Trade Center
SD = standard deviation
Table 3.4: Characteristics of study population of FDNY firefighters by cumulative exposure to radiation by end of follow-up

<table>
<thead>
<tr>
<th>Cumulative exposure to radiation by end of follow-up</th>
<th>≤5.0 mSv(^a)</th>
<th>5.1 mSv-10.0 mSv</th>
<th>10.1 mSv or greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11,631 (79.0%)</td>
<td>1,908 (13.0%)</td>
<td>1,185 (8.1%)</td>
</tr>
<tr>
<td>WTC exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>6,787 (89.8%)</td>
<td>461 (6.1%)</td>
<td>290 (3.8%)</td>
</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>4,826 (67.3%)</td>
<td>1,447 (20.2%)</td>
<td>895 (12.5%)</td>
</tr>
<tr>
<td>Age on 9/11/2001, mean years (SD)</td>
<td>33.8 (10.2)</td>
<td>39.6 (11.7)</td>
<td>42.0 (11.6)</td>
</tr>
<tr>
<td>Number of medical exams by end of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8 exams</td>
<td>752 (95.0%)</td>
<td>29 (3.7%)</td>
<td>11 (1.4%)</td>
</tr>
<tr>
<td>9-28 exams</td>
<td>2,983 (82.8%)</td>
<td>339 (9.4%)</td>
<td>283 (7.9%)</td>
</tr>
<tr>
<td>29-45 exams</td>
<td>2,844 (80.7%)</td>
<td>395 (11.2%)</td>
<td>285 (8.1%)</td>
</tr>
<tr>
<td>46-67 exams</td>
<td>2,805 (78.1%)</td>
<td>488 (13.6%)</td>
<td>300 (8.4%)</td>
</tr>
<tr>
<td>68 or greater exams</td>
<td>2,247 (70.0%)</td>
<td>657 (34.4%)</td>
<td>306 (9.5%)</td>
</tr>
<tr>
<td>Smoking Status by end of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>7,503 (80.3%)</td>
<td>1,148 (12.3%)</td>
<td>692 (7.4%)</td>
</tr>
<tr>
<td>Ever</td>
<td>4,128 (76.7%)</td>
<td>760 (14.1%)</td>
<td>493 (9.2%)</td>
</tr>
<tr>
<td>Diagnosis of thyroid cancer</td>
<td>27 (81.8%)</td>
<td>2 (6.1%)</td>
<td>4 (12.1%)</td>
</tr>
</tbody>
</table>

\(^a\)Combines 0-2.4 mSv and 2.5 mSv-5.0 mSv categories into one level

Abbreviations:
FDNY = Fire Department of the City of New York
mSv = millisieverts
WTC = World Trade Center
SD = standard deviation
Table 3.5: The Risk of Thyroid Cancer by Cumulative Exposure to Radiation from Diagnostic Procedures (Continuous Measure) among FDNY firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% Confidence Interval</td>
<td>P value</td>
<td>Hazard Ratio</td>
<td>95% Confidence Interval</td>
<td>P value</td>
</tr>
<tr>
<td>Cumulative exposure to radiation in mSv (continuous, time-dependent measure)</td>
<td>1.04</td>
<td>0.96-1.10</td>
<td>0.25</td>
<td>1.02</td>
<td>0.93-1.08</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* Adjusted for Age on 9/11/2001 in years and World Trade Center exposure. See Appendix Table 3.5 in the Appendix for related estimates.

Abbreviations:
FDNY = Fire Department of the City of New York
mSv = millisieverts
WTC=World Trade Center
Table 3.6: The Risk of Thyroid Cancer by Cumulative Exposure to Radiation from Diagnostic Procedures (Secondary and Sensitivity Analyses) among FDNY firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Hazard Ratio</th>
<th>Unadjusted 95% Confidence Interval</th>
<th>P value</th>
<th>Adjusted* 95% Confidence Interval</th>
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* Adjusted for Age on 9/11/2001 in yrs and World Trade Center exposure; Abbreviations: FDNY=Fire Department of the City of New York; mSv = millisieverts
Chapter 4: Assessing the Mediating Effect of Increased Medical Attention on the Observed Association between World Trade Center exposure and Thyroid Cancer

4.1. Introduction

The attacks on the World Trade Center (WTC) on September 11, 2001 (hereafter 9/11) and the months of rescue and recovery efforts that followed exposed tens of thousands of individuals to many potentially harmful compounds. These exposures from the dust that resulted from the collapse of the buildings, known as “WTC dust”, as well as from the fires that burned through December 2001 included pulverized cement, glass fibers, asbestos, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and polychlorinated furans and dioxins.\textsuperscript{1-4} Since 9/11 we, and others, have documented a positive association of WTC-exposure with some health conditions. Primarily these associations have been among aerodigestive illnesses, such as asthma and rhinosinusitis,\textsuperscript{5-11} and post-traumatic stress disorder\textsuperscript{5,10,12-14} but recently a limited body of papers has demonstrated a possible association with cancer as well.\textsuperscript{15-18}

The three main studies that have investigated the association of WTC-exposure with cancer reported slightly elevated but non-statistically significant rates of all cancers combined when compared with the general population (standardized incidence ratios [SIR] ranging from 1.02 to 1.14).\textsuperscript{15,16,18} Some cancer types however, were statistically significantly elevated among WTC-exposed rescue recovery workers with larger magnitudes of association; one cancer in particular was thyroid cancer. The Fire Department of the City of New York (FDNY) reported the incidence of thyroid cancer among WTC-exposed firefighters based on 17 cases to be more than
twice the overall rate among men in the United States adjusting for age and race/ethnicity. The SIR for thyroid cancer was 3.07 (95% CI 1.86-5.08); after correcting for potential increased medical surveillance the SIR was reduced to 2.17 (95% CI 1.23-3.82). The method used to correct for possible increased surveillance in the population involved reviewing cases that were diagnosed within six months of a chest computerized tomography (CT) scans or routine FDNY blood tests and, if determined to be incidentally detected based on medical notes, the date of diagnosis was delayed by two years; the two year lag was determined based on screening related lead time among those with prostate cancer. This analysis was done because WTC-exposed firefighters are likely to receive more medical attention than the general population as a result of free care provide by the FDNY Bureau of Health Services (BHS). Elevated rates of thyroid cancer were also observed in the other two WTC-exposed rescue/recovery cohorts (SIR=2.02; 95% CI 1.07-3.45 and SIR=3.12; 95% CI 2.04-4.57), however these studies did not correct for possible surveillance bias. None of these studies analyzed the association between higher levels of WTC exposure and thyroid cancer.

While some of the WTC exposures are known carcinogens, none of the identified compounds has been linked to causing thyroid cancer. The most widely recognized causal factor for thyroid cancer is exposure to ionizing radiation but only normally-occurring baseline levels were reported at the WTC site after the disaster. Nationally, thyroid cancer incidence rates have been increasing, with some evidence suggesting that the rise in thyroid cancer incidence may be related to medical advancements that have improved the detection. Asymptomatic thyroid cancer can also be diagnosed during tests for other unrelated medical conditions or even during routine medical exams. It is estimated that during a CT scan of the neck or chest thyroid
nODULES ARE INCIDENTALLY DETECTED UP TO 17% OF THE TIME, RESULTING IN A POTENTIAL DIAGNOSIS OF CANcer THAT MAY OTHERWISE HAVE BEEN DIAGNOSED LATER OR NEVER DIAGNOSED. One study found that nearly 10% of incidentally detected thyroid nodules were malignant. 

A recent randomized controlled study of low dose CT screening for lung cancer found among individuals assigned to receive chest CT scans the rate of thyroid cancer was two times higher compared with individuals who did not receive CT scans (hazard ratio [HR]=2.19; 95% CI: 1.07-4.47). The study concluded that the difference was a result of incidentally detected thyroid cancer cases during screening using CT scans.

A medical chart review of the cases of thyroid cancer included in the FDNY cancer study revealed that at least five cases may have been detected incidentally during routine medical screening as a result of the WTC disaster. The aim of the current study was to formally assess whether the previously-observed association between WTC exposure and thyroid cancer diagnoses is mediated through increased medical attention. The FDNY firefighter cohort provides a unique opportunity to investigate this study aim because free medical care is available to the population, medical records for the population are available being at date of hire (for most before 9/11) as well as free CT screening was offered to WTC-exposed firefighters.

4.2. Methods

4.2.1. Study Population

The study cohort was selected from the population of FDNY firefighters who were active on 9/11 in addition to those hired between 9/11 and the end of the study, 12/31/2013 (n=16,454). Firefighters who retired before the start of the study were excluded because some FDNY medical
records were incomplete prior to 9/11. Additionally, 137 firefighters with a history of cancer before the start of follow-up were excluded because treatment for cancer, such as radiation therapy, may increase the risk of a subsequent cancer.\textsuperscript{25,37} Non-white firefighters were excluded due small numbers and well-documented differences in thyroid cancer incidence rates in the United States (n=1,552).\textsuperscript{29} Lastly, due to small numbers females (n=41) were excluded, resulting in the final study population of 14,724 non-Hispanic white, male firefighters.

4.2.2. Exposure

Through the FDNY-BHS, active and retired firefighters receive monitoring exams approximately every 12-18 months. The self-administered health questionnaires, which began in 2001, were administered on computers during the monitoring exams and data were also recorded electronically. Self-reported WTC exposure was obtained from the questionnaires. WTC exposure for this study was defined as being present at the WTC disaster site on 9/11 or not. Participants missing WTC exposure information were classified as being not present at the WTC disaster site on 9/11 (n=190).

4.2.3. Outcome

FDNY maintains an internal cancer registry, which acquires information on cancer cases among active and retired FDNY firefighters from two sources. First, the largest source of cases comes from biennial matches to nine state cancer registries including New York, Florida, Pennsylvania, North Carolina, Virginia, New Jersey, Connecticut, South Carolina, and Arizona, states selected for being places where the greatest proportion of firefighters move after retirement, all active firefighters must live in New York. Second, cancer cases were also self-reported on the health
questionnaire or reported to a FDNY physician during a medical evaluation, and therefore captured in the electronic medical record. A trained clinician contacts all participants who reported a cancer not already received during matches to state cancer registries and requests documentation. As with cases from state cancer registries, FDNY confirmation requires a pathology report or detailed treating physician notes/evaluations (operative reports, oncology notes with diagnosis/treatment, formal consultations from related specialists, and/or physical findings consistent with oncologic treatments/modalities). Incident cases of malignant thyroid cancer (ICD-O-3 site code C739) from either a state cancer registry source or confirmed by FDNY diagnosed during the study period were included as the outcome of interest.

4.2.4. Mediators

Medical procedures related to increased medical attention can lead to the incidental detection of thyroid cancer that would otherwise not have been detected. Two measures were used to capture the potential mediating effect of increased medical attention on the association between WTC exposure and the diagnosis of thyroid cancer.

The first mediator of interest in this study was increased medical attention as measured by use of diagnostic procedures, represented by CT scans, because of the potential of incidentally detecting thyroid cancer during CT scan. Chest CT scans, sinus CT scans, and CT/PET scans, which are not performed to diagnose suspected thyroid cancer, were conducted by FDNY among symptomatic patients when clinically needed, typically in response to a variety of respiratory symptoms which do not overlap with symptoms of thyroid cancer unless the tumor is very large. Additionally, firefighters who were present at the WTC site on 9/11 were offered a
screening chest CT scan as part of a screening program to assess for lung abnormalities. FDNY medical records, which contain information on all procedures conducted or paid for by FDNY, were reviewed to obtain the dates of CT scans firefighters received during the study period. CT scans were examined as a dichotomous variable, indicating whether or not a participant had received at least one CT scan.

A second measure of potential increased medical attention was number of FDNY-BHS physician exams. At FDNY-BHS firefighters receive free treatment exams for WTC related health conditions such as asthma, gastroesophageal reflux disease and rhinosinusitis; these medical exams occur either by physician referral or self-referral. When necessary, a firefighter will be referred to an external specialist, for example an ear, nose and throat specialist where additional procedures that can result in an incidental diagnosis of cancer may be conducted. All data, including date of exam, from the FDNY-BHS medical exams were recorded in FDNY’s electronic medical record; external referral information was not available for the whole study period. The total number of FDNY medical exams during follow-up was categorized as tertiles (0-3 exams, 4-8 exams, and 9-129 exams).

4.2.5. Additional Demographic Variables

Demographic data including age on of 9/11 were obtained from the FDNY employee database. Self-reported smoking status was defined as ever if the participant answered positively to being a current or former smoker on any of the self-administered health questionnaires. If a participant consistently answered never smoking, he was defined as a never smoker. Additionally, 201
participants who were missing information regarding smoking status were included as never smokers.

4.2.6. Directed Acyclic Graph

The hypothesized causal pathway for the analyses is shown in Figure 4.1. CT scans and FDNY-BHS medical exams are the two mediators of interest and age on 9/11 is included as the only potential confounder. Sex and race/ethnicity were not included as possible confounders because the analyses are restricted to non-Hispanic white male firefighters. Additionally, smoking is unlikely to have caused WTC exposure so it does not satisfy the definition of a confounder.

4.2.7. Statistical Analysis

Person-time at risk began on 9/11, or date of hire if later. Among participants who were active firefighters at the end of the study, 12/31/2013, follow-up ended on earliest date of either the first cancer diagnosis (thyroid or other cancer) or 12/31/2013. Follow-up was censored for all participants at the diagnosis of any cancer because some cancer treatments may increase the risk of thyroid cancer.\textsuperscript{25,37} For participants who retired during the study period, regardless of state of residence, follow-up ended on earliest date of the following events: first cancer diagnosis (thyroid or other cancer), the last date of contact, or 12/31/2013; the last date of contact was defined as either the retirement date or the last medical exam, depending on which occurred last. Retired firefighters without a current medical exam, within the two years prior to the end of the study, were considered lost to follow-up (n=1,247, 8%) and were censored at the last date of contact.
In order for a variable to be considered a mediator, it needs to be caused by the exposure and to cause the outcome to occur.\textsuperscript{39-42} The associations between WTC exposure and the mediators (CT scans and medical exams) were tested using the Pearson chi-squared test. A Cox regression model with calendar time as the underlying time variable was used to determine the relationship between each mediator and thyroid cancer. The mediating effect was estimated by comparing the total effect of the relationship between WTC exposure and thyroid cancer to the direct effect controlling for the mediator, both the total and direct effects were also adjusted for potential confounders. With survival analysis it has been suggested that an additive model or an accelerated failure time model are the most appropriate models for assessing mediation,\textsuperscript{40} a proportional hazards model can be used when the event is rare.\textsuperscript{43} Because thyroid cancer is a rare event, the mediating role of CT scans and medical exams in the association between WTC exposure and thyroid cancer was evaluated using proportional hazards models. The Cox models were first fit to control for age on 9/11 as a confounder to assess the total effect after controlling for confounding. Then each potential mediator as a time-dependent variable was included in the model to estimate the direct effect. The proportion of mediation associated with CT scans and medical exams, together and separately, was calculated by 1-(direct effect/total effect)\textsuperscript{39} and 95% confidence intervals for the proportions were computed from the 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentile values obtained through bootstrap simulations.\textsuperscript{44} Mediation analyses were first conducted using the time-dependent variable for CT scans where the mediation variable was positive at the time of the first CT scan and remained at the same level for the rest of follow-up. The analyses were then repeated using the time-dependent categorical variable for medical exams where the mediation variable increased a level on the date of the exam that caused the cumulative number of exams to correspond to the next category. The possible exposure-mediator interaction between
WTC exposure and the proposed mediators on the risk of thyroid cancer was also investigated using a Cox model. HRs and 95% CIs were calculated from the models. P-values less than 0.05 were considered statistically significant.

We conducted two sensitivity analyses. Because participants may have received CT scans that were not conducted by FDNY, the first analysis included all self-reported CT scans in addition to the CT scans conducted by FDNY. Self-report of CT scans was obtained from the self-administered health questionnaires which beginning in 2005 included a question about ever receiving a chest and/or sinus CT scans. Since the exact date of the CT scans was not known, the earliest of the following was used: six months prior to the first report of either a chest or sinus CT scan or six months prior to the end of follow-up. The primary analyses were repeated with self-reported CT scans included. The second analysis repeated the primary analyses using Weibull parametric survival model to assess the sensitivity of the findings to the selection of a Cox model analytic approach.

Based on the sample size and the number of thyroid cancer cases, it was expected that we would have 80% power to detect a HR of 2.97 between those present at the WTC site on 9/11/2001 and those not present, assuming the correlation with age was 0.2.

Analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and STATA (version 13; StataCorp LP, College Station, TX, USA). The institutional review boards for The Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; and for the City University of New York, New York, NY approved this study.
4.3. Results

The study population characteristics for the 14,724 firefighters are shown in Table 4.1 by WTC exposure. Forty-nine percent (n=7,168) of the study population was present at the WTC site on 9/11. Of the remaining 51%, 4,017 firefighters (27% of the study population) were never exposed to the WTC site. Participants who were present on 9/11 were on average older than participants who were not present at the time (39.46 years verses 31.25 years; p<0.0001). Those present at the site on 9/11 were also more likely to be an active firefighter with FDNY on 9/11 and to retire by the end of follow-up compared with those not present at that time. The majority of the cohort never smoked by the end of follow-up and smoking status did not differ by WTC-exposure status. Additionally, of the 33 thyroid cancers diagnosed during the follow-up, 23 were among participants who were present at the WTC site on 9/11. The unadjusted association between WTC exposure and thyroid cancer shown in Table 4.2 was statistically significant (HR=2.19, 95% CI 1.04-4.62). After adjusting for age on 9/11 as a confounder the association of WTC exposure with thyroid cancer was no longer statistically significant but it remained elevated (HR=1.75 95% CI 0.80-3.82).

4.3.1. Mediating Role of Increased Medical Attention

In terms of exposure-mediator associations, the proportion of participants with at least one CT scan by the end of follow-up was higher among those present on 9/11 (42.82% among those present on 9/11 versus 15.59% among those not present on 9/11; p<0.0001). Participants who were present on 9/11 also had more medical exams by the end of follow-up than those not present at the time (p<0.0001). In the mediator-outcome analyses, CT scans, as a time-dependent
variable, was statistically significantly associated with thyroid cancer (HR=2.88, 95% CI 1.34-6.17). The association between medical exams and thyroid cancer was elevated but not statistically significant for either level of exams compared with the lowest level (HR for highest level = 2.27, 95% CI 0.89-5.80 and HR for moderate level = 1.56, 95% CI 0.68-3.59). Interaction terms between WTC exposure and the mediators were tested and found to not be significant, thus were not included in the further analyses.

The direct effect, as measured by hazard ratios, between WTC exposure and thyroid cancer when adjusted for CT scans was attenuated from 1.75 to 1.56 (95% CI 0.71-3.43), with CT scans accounting for 19.8% of the observed association (95% CI 0-100%) (Table 4.3). When medical exams was instead included as a mediator, the proportion of the association between WTC exposure and thyroid cancer that was mediated was 11.3% (95% CI 0-100%) (Table 4.3), with an association of WTC exposure with thyroid cancer of was 1.64 (95% CI 0.75-3.60). When CT scans and medical exams were included together in the model the direct effect and proportion of mediation were similar to the model including CT scans as the only mediator, with a hazard ratio of 1.57 (95% CI 0.71-3.45) and 21.9% (95% CI 0-100%) of the association mediated by medical attention (Table 4.3).

Only 62% of those who self-reported a CT scan were confirmed to have received a CT scan though FDNY using medical records, so we repeated the analysis taking self-reported CT scans into account. An additional 883 participants self-reported a CT scan not conducted or captured by FDNY, five of whom also had a thyroid cancer diagnosis. The direct effect, as measured by the hazard ratio, between WTC exposure and thyroid cancer when self-reported CT scans were
also included in the model was 1.42 (95% CI 0.65-3.11), with CT scans accounting for 37.4% of the observed association (95% CI 0-100%) (Table 4.4). When CT scans and medical exams were included together in the model the direct effect was 1.43 (95% CI 0.65-3.14) and proportion of mediation was 36.3% (95% CI 0-100%).

Results from the sensitivity analysis repeating the analyses using a Weibull parametric survival model rather than the Cox model are shown in Tables 4.5, and 4.6. The total and direct effects and the proportion mediated by CT scans were similar to the results from the main analyses. Further, the shape parameter for the Weibull model was near 1 for all models suggesting the baseline risk was roughly constant over time.

4.4. Discussion

Despite the findings from three prior studies suggesting elevated thyroid cancer rates in WTC-exposed cohorts compared with general population rates, this is the first study to specifically investigate the association between greater intensity of WTC exposure and thyroid cancer within directly affected individuals. First, we found that, once age-adjusted, the observed association between being present at the WTC site on 9/11 and a diagnosis of thyroid cancer was not statistically significant. However, the hazard ratio was higher than 1 and the small number of cases resulted in a wide confidence interval, meaning that even moderately large associations cannot be ruled out. In this study, we hypothesized that some of this persistent observed higher risk may be due to the high levels of medical attention populations, such as firefighters, receive as a result of their WTC exposure. Using measures available to us, we found that greater medical attention may account for up to one-third of the remaining higher risk. These results
demonstrate that the WTC exposure-thyroid cancer risk association previously observed is likely due in part to age and increased medical attention, used as an imperfect measure of detection bias.

The risk of thyroid cancer among firefighters who were present at the WTC site on 9/11 was higher compared with the risk among other FDNY firefighters controlling for age however, the association was not statistically significant. This association remained higher in the final models controlling for medical attention but was sizably attenuated. The current findings should be interpreted in the context of information regarding the biologic plausibility of such exposure causing thyroid cancer. Currently, other than exposure to radiation, which was not elevated at the WTC site, there is a paucity of information regarding environmental exposures and thyroid cancer risk. Some of the compounds such as PBCs and asbestos that were present in the WTC dust are known carcinogens, however no link to thyroid cancer has been established.\textsuperscript{20,21} One study hypothesized based on animal models that polybrominated diphenyl ethers (PBDEs) may cause thyroid cancer but it has yet to be documented in humans.\textsuperscript{45} PBDEs were present in small concentrations at the WTC site.\textsuperscript{4}

Examination and analysis of self-reported CT scan information demonstrated that our measure of medical attention defined by CT scans conducted by FDNY and FDNY-BHS medical exams most likely underestimated the true number of CT scans and medical exams in this population. Participants sometime received additional medical attention from non-FDNY healthcare providers, which may also have resulted in an incidental detection of thyroid cancer. Of the 33 thyroid cancer cases, only 11 had a CT scan conducted by FDNY; another five cancer cases self-
reported CT scans outside of the FDNY system, however, the exact timing in relation to the cancer diagnosis is unknown. It is possible that even more CT scans were performed and not captured by our medical or survey data collection efforts. We were also unable to fully estimate the extent of additional medical attention from non-FDNY healthcare providers using medical records, thus both of our measures of medical attention are likely to be underestimated. As a result of this measurement error, the true proportion of meditation may be higher than found in the analyses.

The two main limitations of this study include possible measurement error among the mediators used in the analyses and the lack of statistical power. We observed only 33 cases among over 14,000 firefighters over a 12-year time period. While the association between WTC exposure and thyroid cancer remained slightly higher in the final models, it was no longer statistically significant and we lacked statistical power to detect a significant HR less than 2.97. Additionally, the study period of about 12 years may also not have been long enough to detect thyroid cancer risk. In particular, due to a potential delay in case conformation, we may have underestimated the number of thyroid cancer cases during the last year of follow-up. More time may be needed before fully understanding the association between WTC exposure and thyroid cancer and medical attention as a mediator.

Despite these limitations, this study has a number of strengths. First, even though the number of CT scans may have been underestimated and therefore our measure of detection bias may be inadequate, it is thought that most firefighters receive CT scans through FDNY because FDNY pays for all CT scans and therefore the firefighters have an incentive not to receive a scan from
an outside provider. Second, the methods used to assess increased surveillance among the WTC-exposed firefighters improve upon those used in the first FDNY cancer study. By using an internal comparison group rather than the general United States male population, we were able to account for increased medical attention, which could lead to incidental detection of thyroid cancer. Additionally, the two-year lag used in the first FDNY cancer study to account for increased surveillance was appropriate for some of the types of cancers included in the analyses however, thyroid cancer may not become symptomatic for many years. In fact, one study detected thyroid cancer in about 30% of autopsies suggesting thyroid cancer cases can go undetected for years and possibly a lifetime. In this current study, we were able to address the potential mediation by medical attention with an appropriate reference population.

In our study with only 33 cases of thyroid cancer among FDNY firefighters, we found a potential association between WTC exposure and thyroid cancer to be partially mediated by medical attention. Further studies are needed to determine whether previously observed associations were the result of chance, uncontrolled confounders, and/or as incidental detection from increased medical attention. Future studies involving this and other populations with access to increased cancer surveillance should address the potential for incidental detection when assessing cancer risk.
Figure 4.1: Directed Acyclic Graph for the association between World Trade Center exposure and Thyroid Cancer Diagnoses

Abbreviations:
WTC = World Trade Center
FDNY-BHS = Fire Department of the City of New York Bureau of Health Services
CT = computerized tomography
Table 4.1: Characteristics of Study Population of FDNY firefighters by World Trade Center Exposure Status

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*Follow-up ended at the earliest of date of the following events: first cancer diagnosis (thyroid or other cancer), the last date of contact, or 12/31/2013.

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
SD=standard deviation
Table 4.2: Primary Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Unadjusted</th>
<th>Adjusting for Age*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>WTC exposure on 9/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>23</td>
<td>81,443</td>
<td>2.19</td>
<td>1.04-4.62</td>
</tr>
</tbody>
</table>

*Adjusted for Age on 9/11/2001 in years. See Appendix Table 4.2 in the Appendix for related estimate.

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Table 4.3 Primary Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters Controlling for Potential Mediators

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Model with CT Scan Only Adjusting for Age*</th>
<th>% of mediation</th>
<th>Model with Medical Exams Only Adjusting for Age</th>
<th>% of mediation</th>
<th>Model with CT Scan and Medial Exams Adjusting for Age</th>
<th>% of mediation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTC exposure on 9/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>23</td>
<td>81,443</td>
<td>1.57</td>
<td>0.71-3.44</td>
<td>0.26</td>
<td>19.80%</td>
<td>1.64</td>
<td>0.75-3.60</td>
</tr>
</tbody>
</table>

*Adjusted for Age on 9/11/2001 in years and potential mediators. See Appendix Table 4.3 in the Appendix for related estimates.

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Table 4.4: Sensitivity Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters including Self-Reported CT Scans

<table>
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<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Model with CT Scan Only Adjusting for Age*</th>
<th>Model with CT Scan and Medial Exams Adjusting for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>WTC exposure on 9/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
</tr>
<tr>
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<td>1.42</td>
<td>0.65-3.11</td>
</tr>
</tbody>
</table>

*Adjusted for Age on 9/11/2001 in years and potential mediators. See Appendix Table 4.4 in the Appendix for related estimates.

Abbreviations:
FDNY = Fire Department of the City of New York
WTC = World Trade Center
HR = Hazard Ratio
CI = Confidence Interval
Table 4.5: Sensitivity Analysis with Weibull Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Unadjusted</th>
<th></th>
<th>Adjusting for Age*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P value</td>
<td>HR 95% CI</td>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WTC exposure on 9/11</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>23</td>
<td>81,443</td>
<td>2.17</td>
<td>1.03-4.57</td>
<td>0.04</td>
<td>1.74</td>
</tr>
</tbody>
</table>

*Adjusted for Age on 9/11/2001 in years. See Appendix Table 4.5 in the Appendix for related estimate.

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Table 4.6 Sensitivity Analysis with Weibull Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters Controlling for Potential Mediator

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Model with CT Scan Only Adjusting for Age*</th>
<th></th>
<th>Model with Medical Exams Only Adjusting for Age</th>
<th></th>
<th>Model with CT Scan and Medical Exams Adjusting for Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI P value % of mediation</td>
<td></td>
<td>HR 95% CI P value % of mediation</td>
<td></td>
<td>HR 95% CI P value % of mediation</td>
<td></td>
</tr>
<tr>
<td>WTC exposure on 9/11</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Not present</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>23</td>
<td>81,443</td>
<td>1.56 0.71-3.43 0.27 19.80%</td>
<td></td>
<td>1.64 0.75-3.60 0.21 10.70%</td>
<td></td>
<td>1.55 0.70-3.41 0.28 21.30%</td>
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</tr>
</tbody>
</table>

*Adjusted for Age on 9/11/2001 in years and potential mediators. See Appendix Table 4.6 in the Appendix for related estimates.

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Chapter 5: Discussion

5.1. Overview of Dissertation

The overarching goal of this dissertation was to investigate the possible association between increased use of diagnostic procedures, such as computer tomography (CT) scans, and thyroid cancer risk to assess whether such procedures are contributing to the observed increased in incidence, either causally through radiation exposure or through incidental detection. Two study populations where used in this dissertation. For Chapter 2, United States cancer data was used to examine national trends in thyroid cancer incidence over a timespan of nearly 40 years to determine if change in incidence coincided with time periods where the use of diagnostic procedures increased. In Chapters 3 and 4, Fire Department of the City of New York (FDNY) medical data was used to examine the relationship between radiation exposure from diagnostic procedures and thyroid cancer (Chapter 3), as well as to assess whether incidental detection during diagnostic procedures mediated a previously observed association between firefighters exposed to the World Trade Center (WTC) disaster and thyroid cancer.¹

5.2. Summary of Findings

5.2.1. Chapter 2

Data from nine cancer registries, which represent about 9% of the United States population, were used for Chapter 2 analyses. These registries were from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Between 1973 and 2011, more than 66,000 thyroid cancers were diagnosed in these regions, the majority of which were among women (n=49,678, or 75%).
Age-period-cohort analyses including all thyroid cancers diagnosed during the study period showed a full age-period-cohort model fit best for both women and men, suggesting that in addition to age, both period and cohort effects contributed to the observed increase in thyroid cancer incidence. Findings from models restricted to women suggested that the rate of thyroid cancer incidence changed among those in their late 20s, during the calendar period between 1998 and 2002, and for those born in the 1920s, as well as those born in the 1970s. Findings from models restricted to men suggested the same turning points.

The observed turning points for the period effect are consistent with increased medical attention specifically the use of ultrasounds and CT scans, which occurred during this time in the United States. While secondary analyses by size of tumor showed similar turning points for both palpable and non-palpable tumors, one explanation for this is that collection of information on size of tumor started in 1988, around the same time the diagnostic procedures of interest started to be used, and therefore a change in thyroid cancer rates based on size had already begun and a turning point would not be visible. It is likely however that many of the larger tumors (≥2 cm) were also detected incidentally during diagnostic procedures; as such the period effect would mirror the period effect among the non-palpable tumors. If this is true, with more follow-up time the number of asymptomatic larger tumors in the United States population will decrease as the current pool of asymptomatic larger tumors is exhausted and smaller tumors are simultaneously diagnosed. This would result in differing period effects based on tumor size in future analyses with more years of follow-up.
Findings from this study suggest incidental detection is likely influencing the higher rates of thyroid cancer. Some areas for potential future research, including using individual-level data with case history information to understand the causal relationship between increased medical procedure use and thyroid cancer have been identified from these findings. With full case history information, the asymptomatic cases detected incidentally can be identified and the association between diagnostic procedures and thyroid cancer can be investigated further.

5.2.2. Chapter 3

As part of their employment, many professional United States firefighters receive screening X-rays, often approximately every other year, during routine medical exams. In New York City, FDNY firefighters also have access to additional medical care including these screening X-rays and diagnostic procedures such as CT scans, if needed, in part due to the widespread health risks experienced after the firefighters’ response to the WTC attacks. Between 2001 and 2013, 33 out of 14,724 FDNY firefighters were diagnosed with thyroid cancer.

In Chapter 3, radiation levels from these diagnostic procedures were estimated so that the association between cumulative radiation exposure and thyroid cancer could be investigated in this study population. Exposures occurring less than a year before the diagnosis of thyroid cancer or the end of follow-up were excluded to avoid including medical procedures that could have been related to the diagnosis of cancer. Cumulative radiation exposure during follow-up was examined as a time dependent variable.
Using adjusted Cox models, we found the association between radiation exposure from diagnostic procedures and risk of thyroid cancer was not statistically significant, although risk was elevated for those with high levels of radiation exposure, 2% higher per mSv. Among those exposed to the equivalent of at least one CT scan during the study period (>5 mSv), risk of thyroid cancer was 35% higher than those with less radiation exposure although not statistically significant. This level of increased risk is slightly lower than what has been observed among children exposed to at least one CT.\(^4\) However, the average dose among the exposed firefighter was about 10 mSv and the average dose among the exposed children was less than 6 mSv, suggesting that radiation exposure from diagnostic procedures as an adult may not carry the same risk as exposures experienced during childhood.

5.2.3. Chapter 4

Recent studies have observed a positive association between exposure to the WTC disaster site and an increased rate of thyroid cancer, and yet it remains uncertain whether this observed association is causal.\(^1\,5\,6\) Such findings could be a result of detection bias due to increased medical attention and screening as a result of the WTC disaster. In Chapter 4 using the same FDNY firefighter cohort that was used in Chapter 3, we investigated whether the previously observed WTC exposure-thyroid cancer association was related to greater medical attention. Of the 14,724 firefighters in the study, 7,168 (49%) arrived at the WTC site on 9/11/2001, when the dust exposure was high. Of the remaining 7,556 firefighters in the study population, 4,017 were never present at the WTC site.
Two measures of increased medical attention were examined as potential mediators; these included number of CT scans and number of FDNY medical exams. CT scans were included because firefighter who were present at the WTC site on 9/11/2001 were offered a screening CT scan and those with WTC related respiratory symptoms may have been provided a CT scan for diagnostic reasons. As mentioned above, thyroid cancer can be incidentally detected during a CT scan. Medical exams were included as a possible mediator because firefighters may be referred a specialist outside of FDNY and thyroid cancer may be incidentally detected during further workup outside of the FDNY medical system. We found CT scans and medical exams were both partial mediators for the association between WTC exposure and thyroid cancer, and we demonstrated that the association between WTC and thyroid cancer was not statistically significant after controlling for age. This suggests that the previously observed association between WTC exposure and risk of thyroid cancer may have been due in part to incidental detection as a result of increased medical attention.

After adjusting for age, we found that the association between WTC and thyroid cancer was not statistically significant. The magnitude and significance of the result conflicts with findings in three earlier studies,\textsuperscript{1,5,6} potentially due to methodological differences between those studies and this study. First, this study assessed the association between WTC exposure and thyroid cancer using an internal firefighter comparison group while the previous studies compared thyroid cancer rates for all WTC exposed individuals to external general population rates\textsuperscript{1,5,6} (although one of these studies also compared a group of unexposed individuals to external population rates\textsuperscript{1}). By using an internal comparison in the current study, uncontrolled confounders, such as work exposures or diagnostic practices, may have been more comparable and therefore the
reference population used may have been more appropriate. Further, WTC exposure was defined differently in this study than in the earlier studies. We examined those most exposed to the dust cloud (being present at the WTC disaster site on 9/11/2001) and compared this group to all other firefighters (present at the WTC disaster site or not), not only because this group had the highest dose of WTC exposure, but also because these firefighters have been offered more medical attention such as routine screening CT scans through FDNY. The earlier studies defined WTC exposure as being present at least one day at any time, even months later. This difference may have also contributed to the inconsistent results between studies.

5.3. Limitations

Our studies have some limitations. All analyses used observational data. As result, the associations we observed may be influenced by unmeasured and uncontrolled variables. For example in Chapter 2, we were unable to measure medical history information including use of diagnostic procedures in the study population because of this, it was not possible to determine if a thyroid cancer case was diagnosed incidentally or if additional risk factors such as radiation exposure are related to the national increase in thyroid cancer rates. The findings from Chapter 2 were descriptive and therefore we can only speculate that the change in thyroid cancer incidence is associated with the increased use of diagnostic procedures.

Due to the retrospective nature of the observational data used for Chapter 3 analyses, some medical information was available for the FDNY firefighter cohort however the individual dose of radiation for the diagnostic procedures was not recorded. We estimated radiation levels for each diagnostic procedure using published national averages. While our exposure variable was
likely to have measurement error, a sensitivity analysis using the upper bound of national estimates produced similar results, suggesting that an association between adult exposure to radiation during diagnostic procedures and thyroid cancer, regardless of the exact dose of radiation, has yet to be shown.

FDNY firefighters receive free medical care for many conditions including diagnostic procedures for areodigestive conditions, which include chest and sinus CT scans. Despite the free medical care, some firefighters included in this study may have received care outside of FDNY. Additionally, FDNY medical records did not include complete information for diagnostic procedures until 9/11/2001. Due to these two factors the measure of radiation exposure included in Chapter 3 and the two mediators included in Chapter 4, CT scans and medical attention, may be underestimated. This misclassification is assumed to be non-differential by disease status and WTC exposure status and therefore, would equally underestimate the associations analyzed in this study.

The cohort of firefighters may also be influenced by selection bias. For example, there may be a factor that is related to thyroid cancer that also influences a person to become a firefighter and in turn to be exposed to more diagnostic procedures. And as such, the observed association may be elevated. However, it is also possible that the results from Chapters 3 and 4 were influenced by differential loss to follow-up, which could also cause selection bias. We found those who were loss to follow-up (8% of the cohort) were more likely to be older. If radiation exposure (or WTC exposure) and age both caused participants to be censored then it is possible our study findings are biased. In Chapter 3 we found the results were similar when we restricted to cohort to those
active on 9/11/2001 (and as a result older). To further assess the influence of this potential selection bias, we could conduct an analysis using inverse probability weights, but the results from our sensitivity analysis indicate that it is unlikely that our null findings will change.

Also, many of the firefighters are biologically related to each other. We did not control for this or for family history of thyroid cancer, which may have confounded the relationship of interest. It is possible that this or other residual confounding has influenced the results.

Finally, the FDNY firefighter study population included in Chapters 3 and 4 was only white men; firefighters of other races and women were excluded due to small numbers in the source population. Thyroid cancer rates differ by race, sex and age of exposure to radiation. For example, this difference was observed among those exposed to the atomic bombs during World War II, the highest risk of thyroid cancer was observed in females and those with childhood exposure. The findings for this study may not be generalizable to women and other races and those exposed to radiation during childhood.

5.4. Strengths and Public Health Significance

Our studies also have many strengths. To date, analyses in Chapter 2 include the longest follow-up for thyroid cancer in the United States. The additional years of follow-up included in this study contributes to the expanding knowledge of thyroid cancer in the United States and in turn globally the analyses will help provide information on the increasing thyroid cancer trend and the relation of incidental detection. Methodologically, the age-period-cohort methods employed in this Chapter meant thyroid cancer incidence could be analyzed in terms of a period effect as well
as a cohort effect which most of the current studies were not able to do. This enables potential hypotheses related to exposures experienced by many born during the same time, in addition to the current hypotheses related to age and calendar time.9-11

The study population included in Chapters 3 and 4 was a large population with type and dates of radiation exposure and medical attention documented for most. Further, the study population had similar work exposures because they were all FDNY firefighter. They also had similar geographic exposures because FDNY firefighters are required to live in New York City or the surrounding areas while an active firefighter. While residual confounding is still possible, with this homogenous study population, the potential for many uncontrolled confounders has been reduced.

While the association between radiation exposure at high doses and thyroid cancer has been established, we presented findings from one of the few studies that has investigated the association between radiation exposure from diagnostic procedures and thyroid cancer.4,12-15 Many of the current studies investigating the association with radiation exposure during adulthood included self-reported exposure measures and exposure to X-rays only.12-15 More studies such as the current study with well-documented radiation exposure, particularly exposure to CT scans and among adults, are needed to fully understand the risk of thyroid cancer following radiation exposure from diagnostic procedures.16

By using an internal comparison group rather than the general United States male population as the other WTC cancer studies have done when reporting the thyroid cancer risk, we were able to
measure the influence of elevated medical attention, which could be leading to incidental
detection of thyroid cancer. Further, the complete medical record beginning at the time of the
WTC disaster provides a better estimate of medical attention for the FDNY firefighters than
other WTC exposed cohorts could establish. We found increased medical attention partially
explained the observed relationship between WTC exposure and thyroid cancer. This is
important because it is currently assumed that exposure to the WTC site increased an
individuals’ risk of developing thyroid cancer. The findings from this study and others like it will
help to understand the WTC exposure-thyroid cancer relationship, if any.

5.5. Policy Recommendations and Future Research Directions

Results from these studies demonstrate that while a causal association between low dose
radiation from diagnostic procedures and risk of thyroid cancer may still be possible, the recent
increase in thyroid cancer in the United States and among FDNY firefighters might be largely
caused by incidental detection. If many thyroid cancers being diagnosed today are detected
incidentally, a hypothesis which needs to be tested in a study design capable of assessing
causality, then policy recommendations concerning the use of diagnostic tests, screening and
treatment of these thyroid cancers detected among asymptomatic patients are needed. In order
to provide evidence-based recommendations, additional experimental research should be
conducted investigating the association between treatment of these incidentally-detected cancers
and survival. An ideal study for this would be a randomized control trial in which participants
are randomized to receive treatment or not and the progression of the disease is assessed;
because the benefit of treatment for these asymptomatic cancers is currently unknown, it would
be ethical to randomize participants to receive periodic monitoring without treatment.
Additionally, as part of the 9/11 Health Care Act, WTC-exposed individuals receive free medical care and for some this includes chest CT scans. As a result of this medical attention, the number of thyroid cancers diagnosed is likely to increase due to incidental detection. Public health practitioners, health care workers, and lawmakers should take this into consideration when determining causal impacts of WTC exposures on the development of thyroid cancer.

While the risk of thyroid cancer following radiation exposure from a diagnostic procedure was not found to be statistically significant, our findings suggested that there might be small risks for cancer development resulting from exposure to multiple diagnostic procedures and this has been shown in simulated analyses.\textsuperscript{17,18} Given the results from our findings and the simulated analyses, until additional studies have been conducted, the number of diagnostic procedures and the amount of radiation exposure should be limited to what is clinically needed. For example, nationally it is recommended that firefighters receive periodic chest X-rays to detect lung abnormalities.\textsuperscript{3} It is possible that fire departments may reduce the number of X-rays conducted during employment to limit radiation exposure while still providing sufficient health screening.

In conclusion, while more needs to be understood, by assessing thyroid cancer trends in the United States and the association of radiation exposure and medical attention with thyroid cancer, the findings from this study demonstrate the increase in thyroid cancer diagnoses could be related to the greater use of diagnostic procedures through incidental detection and possibly through radiation exposure but the evidence is lacking for the latter.
Appendix

Appendix Table 3.5: The Risk of Thyroid Cancer by Cumulative Exposure to Radiation from Diagnostic Procedures (Continuous Measure) and Potential Confounders among FDNY firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Hazard Ratio</th>
<th>Unadjusted 95% Confidence Interval</th>
<th>P value</th>
<th>Adjusted 95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative exposure to radiation in mSv (continuous, time-dependent measure)</td>
<td>~</td>
<td>~</td>
<td>1.04</td>
<td>0.96-1.10</td>
<td>0.25</td>
<td>1.02</td>
<td>0.65</td>
</tr>
<tr>
<td>WTC exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>23</td>
<td>81,443</td>
<td>2.19</td>
<td>1.07-4.84</td>
<td>0.04</td>
<td>1.73</td>
<td>0.17</td>
</tr>
<tr>
<td>Age on 9/11/2001 (years)</td>
<td>~</td>
<td>~</td>
<td>1.04</td>
<td>1.01-1.08</td>
<td>0.02</td>
<td>1.03</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of medical exams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8 exams</td>
<td>7</td>
<td>39,071</td>
<td>reference</td>
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<td>9-28 exams</td>
<td>14</td>
<td>59,528</td>
<td>1.13</td>
<td>0.43-3.34</td>
<td>0.81</td>
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<td>29-45 exams</td>
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<td>0.74</td>
<td>0.20-2.75</td>
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</tr>
<tr>
<td>46-67 exams</td>
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<td>0.68</td>
<td>0.13-2.98</td>
<td>0.62</td>
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<tr>
<td>68 or greater exams</td>
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<td>8,447</td>
<td>1.93</td>
<td>0.41-8.50</td>
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<td>Smoking Status</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Ever</td>
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<td>1.13</td>
<td>0.55-2.26</td>
<td>0.72</td>
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</tr>
</tbody>
</table>

Abbreviations:
FDNY = Fire Department of the City of New York
mSv = millisieverts
WTC=World Trade Center
Appendix Table 4.2: Primary Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>Unadjusted</th>
<th>Adjusting for Age*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>WTC exposure on 9/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present on 9/11/2001</td>
<td>10</td>
<td>73,167</td>
<td>reference</td>
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</tr>
<tr>
<td>Present on 9/11/2001</td>
<td>23</td>
<td>81,443</td>
<td>2.19</td>
<td>1.04-4.62</td>
</tr>
<tr>
<td>Age on 9/11/2001 (years)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Appendix Table 4.3: Primary Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters Controlling for Potential Mediators

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Person Years</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>% of mediation</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>% of mediation</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>% of mediation</th>
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<td><strong>WTC exposure on 9/11</strong></td>
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<td>reference</td>
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</tr>
<tr>
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<td>81,443</td>
<td>1.57</td>
<td>0.71-3.44</td>
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<td>19.80%</td>
<td>1.64</td>
<td>0.75-3.60</td>
<td>0.21</td>
<td>11.30%</td>
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Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Appendix Table 4.4: Sensitivity Analyses using Cox Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters including Self-Reported CT Scans

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<th>Variable</th>
<th>Number of Cases</th>
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<th>P value</th>
<th>% of mediation</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
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Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Appendix Table 4.5: Sensitivity Analysis with Weibull Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters

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<th>Number of Cases</th>
<th>Person Years</th>
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<th>P value</th>
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Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
Appendix Table 4.6 Sensitivity Analysis with Weibull Model to Assess the Risk of Thyroid Cancer among FDNY Firefighters Controlling for Potential Mediator

<table>
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<th>Variable</th>
<th>Number of Cases</th>
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<th>95% CI</th>
<th>P value</th>
<th>% of mediation</th>
<th>HR</th>
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<td>19.80%</td>
<td>1.64</td>
<td>0.75-3.60</td>
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<td>0.99-1.07</td>
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<td>132,880</td>
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Abbreviations:
FDNY=Fire Department of the City of New York
WTC=World Trade Center
HR=Hazard Ratio
CI = Confidence Interval
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Chapter 1


Chapter 2


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Chapter 4


Chapter 5


