Title Page

Title: Detection and Incidence of Thyroid Cancer among Three Cohorts of WTC-Exposed Rescue and Recovery Workers
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List of Terms and Abbreviations

WTC = World Trade Center

FDNY=Fire Department of the City of New York

Abstract

Title: Detection and Incidence of Thyroid Cancer among Three Cohorts of WTC-Exposed

PI: Rachel Zeig-Owens DrPH, MPH

Background:

We, and others, documented a positive association of World Trade Center (WTC)-exposure with thyroid cancer –at least twice that of the general population – though none of the WTC exposures have been definitively shown to be associated with thyroid cancer; only normally-occurring baseline levels of radiation were reported at the WTC site after the disaster. Nonetheless, the elevated risk of thyroid cancer might be due to WTC-related exposure, such as synergistic chemical effects, exposures to chemicals, or doses not studied in other settings, or it might be due to other factors experienced by the WTC-exposed cohorts, such as incidental detection as a result of increased medical surveillance. This project aimed to quantify the extent to which the association between WTC exposure and thyroid cancer is influenced by increased medical surveillance among WTC-exposed rescue/recovery workers.

Methods:

For the first two aims using data from Fire Department of the City of New York (FDNY) WTC-exposed members of this project we classified the detection method (i.e., incidental vs. symptomatic) of thyroid cancer cases via chart review, and then compared the risk of thyroid cancer, overall, and by detection method (i.e., incidental vs. symptomatic), among FDNY rescue/recovery workers to the risk among demographically similar Olmsted County residents from the Rochester Epidemiology Project (REP).

For the third aim using data from all NYC based WTC-exposed rescue/recovery workers, we compared thyroid cancer risk among rescue/recovery workers in the WTC Health Program to the risk among WTC-exposed rescue/recovery workers not in the WTC Health Program (WTCHP). Person-time began on 9/12/2001 or at enrollment in a WTC cohort and ended at death or 12/31/2015. Cancer data were obtained through linkages with thirteen state cancer registries. We used Poisson regression to estimate rate ratios (RR) and 95% confidence intervals (CI) for WTCHP and non-WTCPH participants. New York State (NYS) rates were used as the reference. To estimate potential changes over time in WTC-associated risk, change points in RRs were estimated using profile likelihood.

Results:

Aims 1&2 results: The overall age-standardized incidence of thyroid cancer was significantly higher in the FDNY cohort: 24.7 (95%CI=17.4-52.3) vs. 10.4 (95%CI=8.5-12.7) per 100,000 in the REP. Overall, the incidence rate of FDNY thyroid cancer was twice that of the REP (Relative Rate (RR)=2.3; 95%CI=1.7-3.2). The rate of incidental cancers was over 3 times greater among FDNY compared with REP (RR=3.2; 95%CI=2.1-4.7). The comparison of FDNY and REP symptomatic rates did not exhibit a significant difference. Aim 3 results: The thyroid cancer rate among WTCPH participants was more than twice that of NYS population rates

(RR=2.31; 95%CI=2.00-2.68). Non-WTCPH participants had a risk similar to NYS (RR=0.96, 95%CI=0.72-1.28). We observed no change points in the follow-up period.

Conclusions:
These findings support the hypothesis that no-cost screening (a benefit provided by WTC-medical monitoring and treatment programs) is associated with elevated identification of thyroid cancer. Given the high survival rate for thyroid cancer, it is important to weigh the costs and benefits of treatment, as many of these cancers were asymptomatic and may have been detected incidentally.

Section 1 of the Final Progress Report
(2 page limit)

Significant or Key Findings

Among Fire Department of the City of New York (FDNY) rescue/recovery workers 80% of the thyroid cancer cases were detected incidentally. When compared with demographically similar Olmsted County residents from the Rochester Epidemiology Project (REP). The rate of incidental cancers was over 3 times greater among FDNY compared with REP (Relative Rate (RR)=3.2; 95% CI=2.1-4.7) while the rate of symptomatic thyroid cancers was not significantly different. When analyses were expanded to all WTC-exposed rescue/recovery workers from FDNY, the General Responder Cohort and the World Trade Center Health Registry, the rate of thyroid cancer was elevated for WTC-exposed rescue/recovery workers who were also in a medical monitoring and treatment program; specifically, the rate of thyroid cancer was greater than two times that of the general New York State population (RR=2.31; 95% CI=2.00-2.68). The rate of thyroid cancer for WTC-exposed rescue/recovery workers who were not in a medical monitoring and treatment program though was similar to the general New York State population (RR=0.96, 95%CI=0.72-1.28).

Translation of Findings

These findings support the hypothesis that no-cost screening (a benefit provided by WTC-medical monitoring and treatment programs) is associated with elevated identification of thyroid cancer. Given the high survival rate for thyroid cancer, it is important to weigh the costs and benefits of treatment, as many of these cancers were asymptomatic and may have been detected incidentally.

Research Outcomes/Impact

The findings from this study can guide the WTC Health Program approach to managing and treating thyroid cancer.

Section 2 of the Final Progress Report

Scientific Report

Specific Aim 1: To classify the detection method (i.e., incidental vs. symptomatic) of thyroid cancer cases via chart review, and to describe how cases detected incidentally compare to symptomatic cases in terms of histological make up, cancer stage and mortality.

Specific Aim 2: To compare the risk of thyroid cancer, overall, and by detection method (i.e., incidental vs. symptomatic), among FDNY rescue/recovery workers to the risk among demographically similar Olmsted County residents from the Rochester Epidemiology Project (REP).

(Aims 1 and 2 were carried out together)

Evaluation of Medical Surveillance and Incidence of Post-September 11, 2001, Thyroid Cancer in World Trade Center–Exposed Firefighters and Emergency Medical Service Workers

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Introduction

Over the past 4 decades, thyroid cancer incidence rates have increased nearly 3-fold,[1,2] resulting in its current status as one of the most commonly diagnosed cancers in the US. During the 1990s, thyroid cancer incidence rates began to increase from an annual age-standardized rate of 4.9 to 14.2 per 100 000 person-years in 2010-2014.[1] Rates among US men (8.0 per 100 000 person-years) are about one-third that of women (23.3 per 100 000 person-years), although mortality rates are similar, at 0.52 vs 0.49 per 100 000 person-years.[1] The increased incidence is primarily limited to the least aggressive histologic type: papillary thyroid cancer.[2,3,4,5,6]

Many studies have concluded that thyroid cancer's increasing incidence is largely owing to the incidental detection of small, asymptomatic lesions associated with improvements in diagnostic imaging,[4,5,7,8,9,10,11] although other studies challenge this theory.[2,12,13,14,15] Studies proposing an increase in incidence often attribute the increase to environmental exposures, such as atmospheric or medical radiation therapy,[14,16] or to excess body mass.[17,18,19]
The large quantity and variety of toxicants released into the environment following the World Trade Center (WTC) terrorist attacks on September 11, 2001 (9/11),[20] may represent an environmental exposure contributing to the 2- to 3-fold greater risk of thyroid cancer among WTC-exposed populations compared with the general population.[21,22,23,24] Two recent studies describe WTC-related thyroid cancers and suggest a true excess risk among WTC responders compared with matched controls.[25,26] While radiation exposure was not reported to be elevated at the WTC site, other known carcinogens, such as polybrominated diphenyl ethers, were present at high levels[20,27,28] and may disrupt mechanisms of thyroid hormone production.[29,30,31] To our knowledge, no chemical substance has been consistently associated with thyroid cancer in

humans. Alternatively, since 9/11, WTC-exposed rescue/recovery workers are provided with annual medical monitoring and treatment visits, which often include chest computed tomographic scans.[21,23] The elevated thyroid cancer rate may therefore be an artifact of such frequent and detailed medical surveillance. The WTC Health Program does not include thyroid screening by ultrasonographic scans unless a nodule is suspected on examination or imaging paid for by the WTC Health Program.

In this study, we assessed whether the association between WTC exposure and thyroid cancer diagnosed between September 12, 2001, and December 31, 2018, in male, WTC-exposed Fire Department of the City of New York (hereafter, Fire Department) firefighters and emergency medical service workers was also associated with medical surveillance. To do so, we determined the rate of thyroid cancer incidence in demographically similar individuals from the Rochester Epidemiology Project, which included all residents of Olmsted County, Minnesota, during a similar period (January 1, 2000, to December 31, 2018). The primary aim of this study was to compare the relative rate of thyroid cancer, overall and by detection method, among Fire Department rescue/recovery workers and Olmsted County residents from the Rochester Epidemiology Project.

Methods

The source population consisted of 15 478 WTC-exposed firefighters and emergency medical service personnel who arrived at the disaster site between the morning of 9/11 and July 25, 2002. Women were excluded (n = 491) owing to the small sample size. The final study population consisted of 14 987 participants (Figure 1). The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board approved this study and waived the need for informed consent because the review of medical records research involves no more than minimal risk to the patients.

Methods used to obtain information on cancer diagnoses from state registries are described elsewhere.[21] Briefly, thyroid cancer diagnoses were ascertained via 2 methods: by linkage to state cancer registries[32] and medical record confirmation of cases reported to the Fire Department Bureau of Health Services. Specifically, confirmation was completed by a trained clinician (N.J.) who contacted participants reporting a cancer not already identified through state cancer registry matches and requested documentation. We required a report of pathologic findings or detailed treating physician notes/evaluations to confirm these cases.[21] Only confirmed thyroid cancers, either by medical records or as obtained from any state cancer registry match, diagnosed between September 12, 2001, and December 31, 2018, were included in this study.
The Fire Department WTC Health Program performs health evaluations on all active and retired WTC-exposed firefighters and emergency medical service workers every 12 to 18 months. Demographic data (race/ethnicity, sex, birth date, and body mass index) and medical testing history before the diagnosis date (chest and sinus computed tomographic scans, magnetic resonance imaging of the head and neck, stress tests, positron emission tomographic scans, cervical imaging, echocardiograms, stress tests, gastrointestinal tract tests, sleep studies, or surgeries) were collected from WTC Health Program records. No demographic data were missing. Level of WTC exposure was defined from the earliest post-9/11 health questionnaire as arriving the morning of 9/11; arriving the afternoon of 9/11; arriving on September 12, 2001;

arriving between September 13 and September 24, 2001; and, arriving between September 25, 2001, and July 25, 2002.[33] Duration of work at the WTC site ranged from 1 to 10 months.[34] Method of thyroid cancer detection was abstracted from medical records and confirmed by one of us (N.J.) during follow-up telephone calls; cases confirmed only by state cancer registry linkages were not included. Abstracted records were then categorized as either an asymptomatic or symptomatic case (Figure 1). Detection method was missing from 7 cases (9.7%). Method of detection was defined according to the criteria used by previous Rochester Epidemiology Project investigations of thyroid cancer incidence (Figure 1).[7] Reliability of categorizations between the Fire Department and Rochester Epidemiology Project[7] investigators was estimated by independent assessment (N.J. from the Fire Department and N.G. from the Rochester Epidemiology Project) of a random subset of 34 Fire Department cases; 100% agreement was found.

The Rochester Epidemiology Project reference cohort, a previous comparison population for WTC-exposed firefighters[35,36] described in detail by Brito et al,[7] has medical records from Olmsted County, Minnesota, residents. Given their geographic distance from New York City (approximately 1300 miles), it is unlikely that Rochester Epidemiology Project participants were WTC exposed. In 2017, Olmsted County had approximately 111 000 adults aged 20 years or older, and 85% of the county was white.[37] In addition, over 90% of Olmsted County residents are evaluated by medical health care professionals in any 3-year period.[38] Occupational history was unavailable.

Rochester Epidemiology Project investigators provided age-, sex-, detection-, and histologic-specific thyroid cancer incidence rates during a similar period (January 1, 2000, to December 31, 2018) as the Fire Department case accrual. Only rates of thyroid cancer in men from this cohort were included in our analysis. The Rochester Epidemiology Project medical record linkage system, validation, and data retrieval processes have been described elsewhere.[7] From each record, demographic characteristics, the date of diagnosis, and histologic codes were abstracted by an experienced retrieval specialist from the Rochester Epidemiology Project. Clinicians (N.G., J.P.B., O.M.E.K.) designated the cases as having asymptomatic or symptomatic detection as defined by Brito et al[7] and detailed above. The Surveillance, Epidemiology, and End Results–21 (SEER-21) program was used to calculate the US male thyroid cancer rate and 95% CIs from January 2000 to December 2016.[39]

Statistical Analysis

Demographic and other characteristics of the study population and detection method subgroups were assessed as proportions, medians, interquartile ranges, and means (SDs), as appropriate. Age-standardized incidence was calculated as the number of confirmed cases per 100 000 person-years. Person-time accrual began on September 12, 2001, or on the Fire Department hire date, whichever occurred later. Follow-up ended on the earliest of the following dates: death, diagnosis of incident thyroid cancer, end of the study (December 31, 2018), or, for retired members, the last Fire Department treatment date or post-9/11 Fire Department medical monitoring visit. Relative rates (RRs) were estimated using Poisson regression models for grouped data, controlling for age group (in 5-year strata). Approximate 95% CIs were calculated for RRs using the Poisson distribution[40] and for direct standardized incidence rates, using the modified γ approximation method,[41] which assumes a Poisson distribution.

Fire Department, Rochester Epidemiology Project, and SEER-21 annual incidence rates were directly standardized to the US 2000 male population aged 20 years and older. The RRs for the Fire Department and Rochester Epidemiology Project were compared in the following analyses: overall, by restricting to asymptomatic cases and then to symptomatic cases, across an early period (September 12, 2001, to December 31, 2009) and a late period (January 1, 2010, to December 31, 2018), and by 3 definitions of WTC exposure based on arrival the morning of 9/11 or later and duration of work at the WTC site.[36] Secondary analyses calculated the same estimates comparing only papillary thyroid cancer cases. We performed 2 sensitivity analyses. First, we conducted the same RR comparisons as the primary analysis but restricted to ages 30 to 79 years since US men's thyroid cancer rates are greatest between ages 30 and 80 years[42,43] and the Fire Department did not identify cases among those aged 20 to 29 or older than 80 years. Second, we recalculated the symptomatic RR comparison of the primary analysis, assuming that all Fire Department cases without a categorized detection method were symptomatic.

Findings were considered significant at 2-sided $P = .05$. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

From September 12, 2001, to December 31, 2018, we identified 72 men with confirmed cases of post-9/11 thyroid cancer. The median age at diagnosis was 50.0 (interquartile range, 44.2-58.2) years and the median time to diagnosis was 11.5 (interquartile range, 6.8-14.5) years post-9/11. None of the men with thyroid cancer who were monitored in the Fire Department program experienced thyroid cancer–specific mortality and none developed metastatic disease. About half of the men (38 [52.8%]) are known to have had unrelated medical testing before their thyroid cancer diagnosis. Demographic characteristics (ie, age and body mass index) of those with and without thyroid cancer were largely similar (eTable 1 in the Supplement), although men without thyroid cancer had a slightly higher proportion of ever-smokers (5514 [37.0%] vs 19 [26.4%]). Furthermore, the characteristics of the Fire Department and Olmsted County 2000 general population were equivalent regarding their median ages (40.0 vs 35.0 years) and race/ethnicity (88.0% vs 90.3% white).[44]

Of the total 72 thyroid cancer cases, 65 cases (90.3%) had an established method of detection (asymptomatic or symptomatic). Compared with symptomatic cases, asymptomatic cases comprised more white individuals (47 [88.7%] vs 10 [83.3%]), firefighters (50 [94.3%] vs 10 [88.3%]), and ever-smokers (15 [28.3%] vs 2 [16.7%]) (Table). Among the 7 cases without a detection method, most (4 [57.1%]) were identified exclusively by state registry matching. Of the 65 patients with categorized cancer, 53 men (81.5%) were asymptomatic and 12 men (18.5%) were symptomatic (Figure 1). The eFigure in the Supplement shows the number of post-9/11 Fire Department cases by year of diagnosis, stratified by detection method. Among the categorized cases, age at diagnosis spanned 30 to 79 years. Fewer than half of the 65 cases were diagnosed in the early period (23 [35.4%]) (September 12, 2001, to December 31, 2009). Papillary thyroid cancer accounted for 52 of 53 (98.1%) of Fire Department cancers with a detection method; only 1 of these was a follicular carcinoma. Overall, 37 cases (57.0%) identified with a detection method had unrelated medical testing before the thyroid cancer

diagnosis. The proportion of patients with asymptomatic cases known to have had unrelated medical testing (62.3%) was almost twice that of those with symptomatic cases (33.3%).
There were 99 Rochester Epidemiology Project thyroid cancer cases, with 54 asymptomatic (54.5%) and 45 symptomatic (45.5%) at detection. The age range at diagnosis was 20 to older than 85 years; the median age was 50.0 (interquartile range, 41.8-61.3) years. Most (92 [92.9%]) of the Rochester Epidemiology Project cases were papillary cancers.
The overall age-standardized incidence of thyroid cancer among men aged 20 years or older was greater in the Fire Department cohort: 24.7 (95% CI, 17.4-52.3) vs 10.4 (95% CI, 8.5-12.7) in the Rochester Epidemiology Project and 9.1 (95% CI, 9.0-9.1) in SEER-21 per 100 000 person-years; asymptomatic cancers accounted for this difference. We observed an apparent interaction between thyroid cancer incidence and age (<50 vs ≥50 years), particularly among symptomatic cases. However, for both age groups, Fire Department asymptomatic age-standardized rates (13.2 per 100 000 for age 20-49 years and 25.1 per 100 000 for ≥50 years) were greater than the total rates for the Rochester Epidemiology Project (6.9 per 100 000 for age 20-49 years and 18.0 per 100 000 for ≥50 years) and SEER-21 (5.9 per 100 000 for age 20-49 years and 14.1 per 100 000 for ≥50 years) (Figure 2A and B). Furthermore, the age groups' crude absolute rates for the detection methods within each cohort were consistent with their respective age-adjusted rates; the one exception was among Fire Department men aged 20 to 49 years, in which undetermined age-adjusted rates were higher than the crude rates (4.4 vs 1.6) and asymptomatic and symptomatic adjusted rates were lower (age-adjusted vs crude: 13.2 vs 18.8 asymptomatic and 3.4 vs 6.3 symptomatic).
Figure 3 shows the post-9/11 incidence of thyroid cancer by age-adjusted relative rates overall, by early and late periods, and by detection method. Overall, the Fire Department thyroid cancer incidence rate was twice that of the rate for the Rochester Epidemiology Project (RR, 2.3; 95% CI, 1.7-3.2). The early time-period RR was moderately different between the Fire Department and Rochester Epidemiology Project (RR, 1.8; 95% CI, 1.1-3.0); however, the Fire Department incidence rate was higher during the late period (RR, 2.5; 95% CI, 1.6-3.8). By detection method, the thyroid cancer rate for the whole period among symptomatic Fire Department cases was not significantly different from that of Rochester Epidemiology Project cases (RR, 0.8; 95% CI, 0.4-1.5); however, there was a larger rate of asymptomatic cancers in the Fire Department cohort (RR, 3.1; 95% CI, 2.1-4.7). The crude RRs for all of the comparisons were slightly larger than their age-adjusted counterparts. Relative rates across all levels of WTC exposure were similar, with no exposure gradient (eTable 2 in the Supplement).

Effect sizes in the secondary analysis restricted to papillary thyroid cancers were similar (eTable 2 in the Supplement). Results from the first sensitivity analysis restricting to men aged 30 to 79 years were analogous to those from the primary and secondary analyses (eTable 2 in the Supplement). In the second sensitivity analysis, the thyroid cancer rate among symptomatic Fire Department cases, including the uncategorized 7 as symptomatic cases, was not significantly different from that of the Rochester Epidemiology Project (RR, 1.3; 95% CI, 0.7-2.3).

Discussion

Previously reported excess thyroid cancer rates among Fire Department WTC-exposed firefighters[21] are likely associated with overdiagnosis owing to medical surveillance. We found that the Fire Department age-standardized incidence rate of asymptomatic cases exceeded the

rate of both our non–WTC-exposed comparison from the Rochester Epidemiology Project and the US general population. Furthermore, we found a significant age-adjusted RR among asymptomatic cancers, in which the Fire Department RR was approximately 3 times greater than that of the Rochester Epidemiology Project. There was no statistically significant difference between Fire Department and Rochester Epidemiology Project rates among symptomatic cases, even assuming that cases without a categorized detection method were symptomatic. In addition, there was no metastatic disease or thyroid cancer–specific deaths among Fire Department cases. Our study provides evidence that the increase in thyroid cancer rates is not owing to clinically apparent disease; rather, we suggest that the predominant factor in the higher WTC incidence rate is asymptomatic thyroid cancers detected incidentally via non–thyroid-related medical surveillance.

There was no significant difference in the Fire Department thyroid cancer incidence compared with the Rochester Epidemiology Project incidence during the early post-9/11 period; however, during the late period (2010-2018), when access to medical care increased with the passage of the James L. Zadroga 9/11 Health and Compensation Act, the Fire Department incidence increased to 2 and a half times that of the Rochester Epidemiology Project. Given that detection of subclinical pools of thyroid cancer lesions can be directly related to health care access,[45] we believe that the totality of our results suggests that incidental detection has played a role in the elevated incidence of WTC-exposed thyroid cancers reported by previous studies.[21,22,23,24] Several other explanations for the higher overall incidence rate of thyroid cancer among the Fire Department compared with the Rochester Epidemiology Project may be suggested. One such explanation is that the incidence of Fire Department cancer cases may be a product of medical radiation exposure.[16] Yet, previous research investigating the risk of thyroid cancer among WTC-exposed firefighters due to radiation exposure from diagnostic procedures was not conclusive, even when comparing the highest level of radiation exposure with the lowest.[46] Another argument is that overweight and obesity may predispose individuals to thyroid cancer. Some cross-sectional studies of patients with papillary thyroid cancer suggest that overweight and obesity are associated with aggressive clinical and pathologic tumor characteristics.[17,18,19] Most Fire Department tumors cannot be characterized as aggressive because we did not observe thyroid cancer–specific mortality or metastatic disease; furthermore, there was no statistically significant difference in the average body mass index between cases and noncases in the Fire Department cohort. In addition, while it was suggested that some physicians may be more likely to diagnose a WTC-exposed patient with thyroid cancer than a non–WTC-exposed patient, at least one study found this not to be the case.[26]

We believe the results of this study have important implications because many thyroid cancers in the Fire Department men were asymptomatic incidentalomas that likely represent a subclinical reservoir of disease and may have been treated via lobectomy or total thyroidectomy. Although not seen in our cohort, complications of thyroidectomy have been seen to arise,[47,48,49] particularly in lower-volume surgical centers, and often require complex medical management.[50] The personal and financial costs of thyroid operations are approximately $35 000 per patient—a price that may increase in the next 10 years.[51] We believe these physical and financial burdens should be considered for patients diagnosed with small, asymptomatic papillary carcinomas discovered on non–thyroid-related imaging, since papillary thyroid cancers have a 5-year cancer-specific survival rate as high as 98%.[8] One strategy to attenuate a high thyroid cancer diagnosis rate was

enacted by South Korea, which began to conduct fewer screenings in March 2014 and since then has experienced fewer diagnoses and surgical operations.[52] Alternatively, the American Thyroid Association has recommended adopting an active surveillance protocol for low-risk papillary microcarcinomas,[53] which could be a treatment option for qualifying WTC-exposed patients.

Limitations and Strengths

Our study had some limitations. First, we lacked a Fire Department, non–WTC-exposed comparison group; however, the male Rochester Epidemiology Project comparison group was similar in terms of demographics, access to care, and study methods.[37,38] Second, given the retrospective extraction of detection method data, both the Fire Department and Rochester Epidemiology Project could have misclassified patients. Information regarding detection method was missing from the medical records of some Fire Department cases. To address this lack of information, the detection method was determined via telephone conversations, and researchers from the Fire Department and Rochester Epidemiology Project discussed all debatable cases to achieve consensus. Differential misclassification was also possible despite efforts to follow the same protocol. However, evidence against misclassification included the full agreement between examiners in the random subset of Fire Department cases and the difference in rates among asymptomatic Fire Department and Rochester Epidemiology Project cases. Third, the Fire Department did not have information on size or staging for all thyroid cancer cases; therefore, we could not compare these characteristics with those of the Rochester Epidemiology Project or the results from other studies. Fourth, our results may not be generalizable to other occupational cohorts given that our population was exclusively male, white, and had above-average physical health prior to WTC exposure.

Despite these limitations, the study strengths are notable. First, to our knowledge, this is the only study to examine thyroid cancer detection methods among WTC-exposed responders. Second, our large, closed cohort was defined before WTC exposure, thereby minimizing enrollment bias. Third, Fire Department and Rochester Epidemiology Project comparison populations were suitably matched; in addition, Rochester Epidemiology Project coinvestigators provided age-, sex-, and histologic-specific rates from a similar period as the collection of Fire Department rates. Fourth, our results underscore the importance of evaluating the characteristics of health care systems when considering the incidence and prevalence rates of specific diagnoses.

Conclusions

The results of this study suggest that a greater number of asymptomatic thyroid cancers have been diagnosed in Fire Department WTC-exposed rescue/recovery workers. The high incidence of thyroid cancer post-9/11 appears to be attributable to the increased diagnosis of occult lesions owing to the detailed and frequent medical testing of WTC-exposed individuals. There seems to be no incidence of disease-specific thyroid cancer mortality, and carcinoma discoveries were largely of the least-aggressive subtypes, suggesting that the observed RRs are due to a greater detection of subclinical cancers in Fire Department rescue/recovery workers than in the comparison population. This finding appears to be supported by the primary and secondary analyses of incidence rates by detection method. Our results have important implications for how

thyroid cancer incidence rates are interpreted and how cases should be managed once diagnosed, not only for WTC-exposed cohorts, but for the general population as well.

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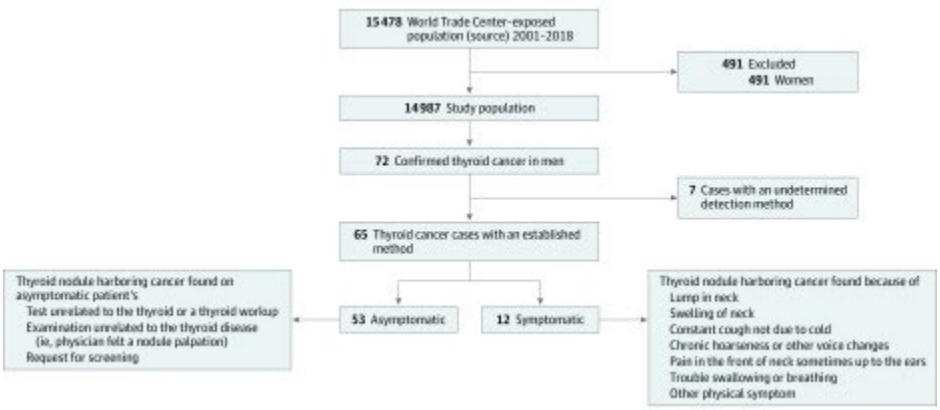
Figure 1. **Detection Method Categorization for Fire Department of the City of New York–Confirmed Thyroid Cancer Cases**



Study population and detection method categorization criteria for Fire Department of the City of New York thyroid cancer cases.

Table.

Demographic and Other Characteristics of the Fire Department of the City of New York Population by Thyroid Cancer Detection Method[a]

Characteristic	No. (%)	
	Asymptomatic cases (n = 53)	Symptomatic cases (n = 12)
WTC arrival group		
Morning of 9/11	9 (17.0)	2 (16.7)
Afternoon of 9/11	25 (47.2)	5 (41.7)
9/12/2001	9 (17.0)	3 (25.0)
9/13/2001-9/24/2001	9 (17.0)	2 (16.7)
After 9/24/2001	1 (1.9)	0
WTC work duration, median (IQR), mo	3 (1.0-6.0)	2.5 (1.5-4.5)
Age on 9/11, median (IQR)	38.8 (32.5-46.8)	36.2 (31.1-41.7)
Race/ethnicity		
White	47 (88.7)	10 (83.3)
Nonwhite	6 (11.3)	2 (16.7)
Current smoking status		
Never smoker	38 (71.7)	10 (83.3)
Ever smoker	15 (28.3)	2 (16.7)
Unknown	0	0
BMI at end of follow-up, mean (SD)[b]	30.9 (3.9)	30.8 (3.2)
Work assignment		
Firefighter	50 (94.3)	10 (83.3)
Emergency medical service	3 (5.7)	2 (16.7)
Died	1 (1.9)	0
Age at diagnosis, median (IQR)	50.2 (44.0-58.6)	46.6 (43.9-52.9)
Range	30.3-76.3	38.2-59.6
Years to diagnosis post-9/11, median (IQR)	12.2 (6.7-14.4)	11.5 (7.8-16.0)
Prediagnostic testing[c]	33 (62.3)	4 (33.3)
Thyroid cancer histologic findings		
Papillary	52 (98.1)	12 (100.0)
Follicular	1 (1.9)	0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; WTC, World Trade Center.

[a]Does not include the 7 cases in which no method of detection could be determined.

[b]Body mass index data only available for 52 asymptomatic cases.

[c]Included chest and sinus computed tomographic scans, sleep studies, gastrointestinal tract tests, echocardiograms, magnetic resonance imaging of the head and neck, stress tests, positron emission tomographic scans, cervical imaging, or surgery.

Figure 2. Age-Standardized Thyroid Cancer Incidence Rates by Cohort and Detection Method

Bar graphs of the total age-standardized thyroid cancer incidence rate (per 100 000 person-years) among men are stratified by those aged 20 to 49 years at diagnosis (A) and those aged 50 years and over (B) from the Fire Department of the City of New York, Rochester Epidemiology Project, Rochester, Minnesota, and the US National Cancer Institute Surveillance Epidemiology and End Results–21 (SEER-21) registries. Data were age-adjusted to the 2000 US standard population.

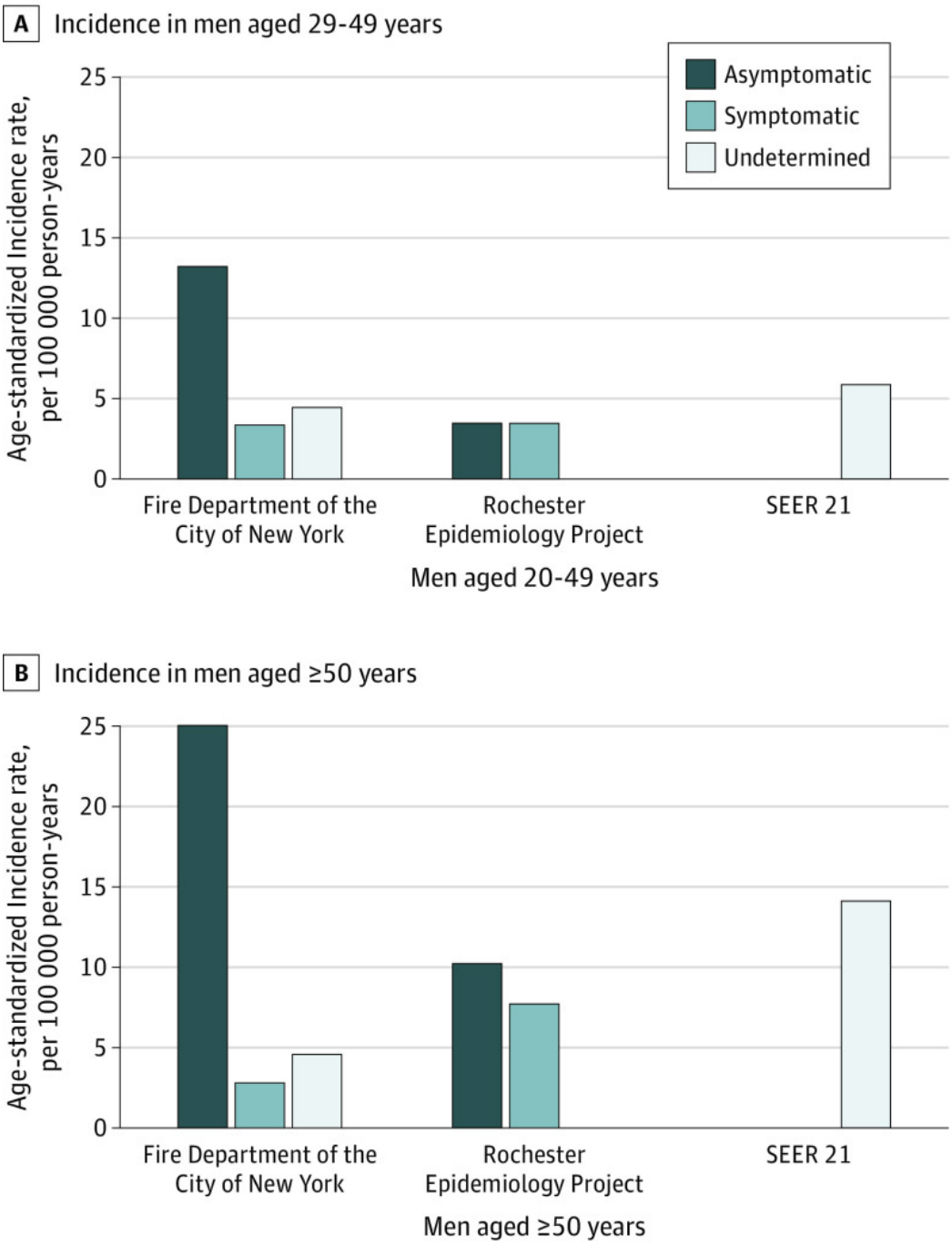
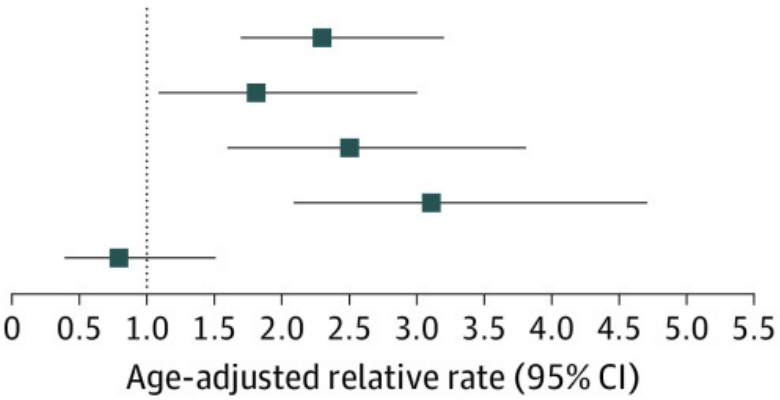


Figure 3. Age-Adjusted Relative Rates (RRs) of Thyroid Cancer Overall, by Early and Late Period, and by Detection Method Comparing Fire Department of the City of New York With the Rochester Epidemiology Project

Variable	Age-adjusted RR (95% CI)
Overall	2.3 (1.7-3.2)
Early period	1.8 (1.1-3.0)
Late period	2.5 (1.6-3.8)
Asymptomatic	3.1 (2.1-4.7)
Symptomatic	0.8 (0.4-1.5)



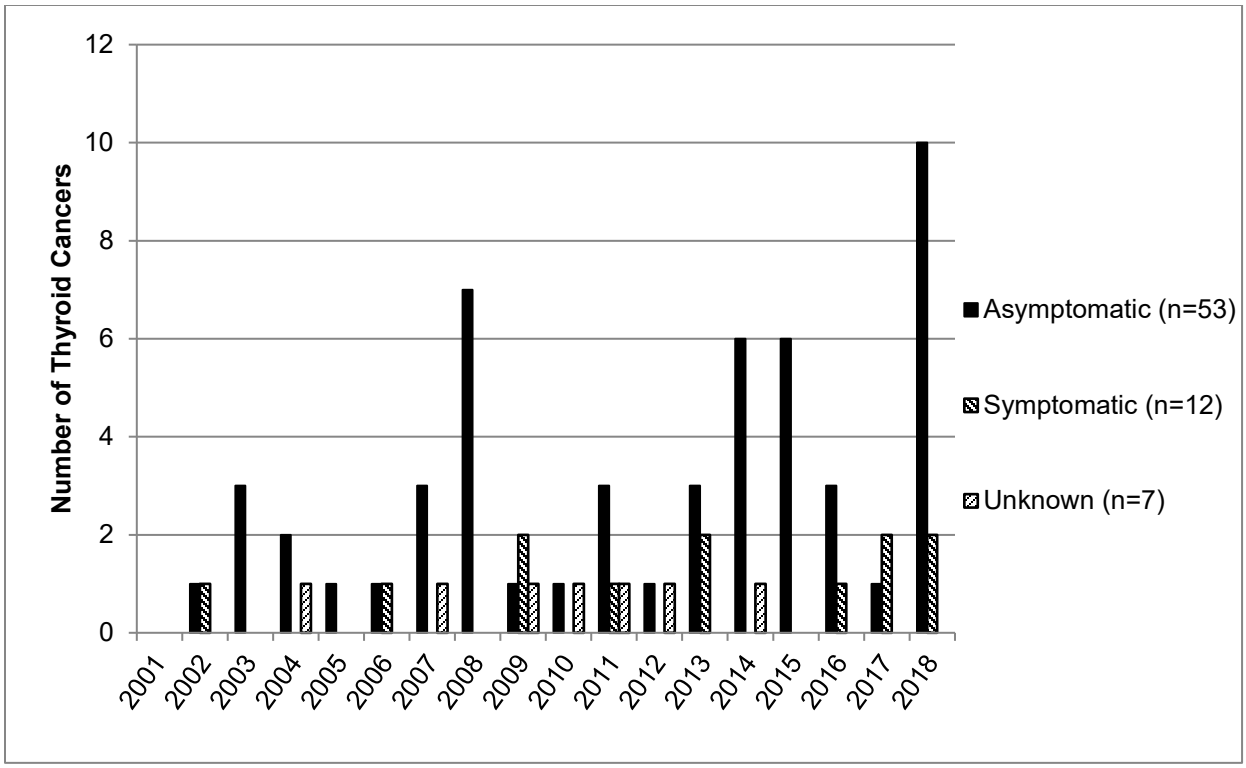
Relative rates, controlling for age group (in 5-year strata), comparing Fire Department of the City of New York and Rochester Epidemiology Project incident thyroid cancer rates, overall, by an early (September 12, 2001, to December 31, 2009) and late (January 1, 2010, to December 31, 2018) period and by detection method (asymptomatic and symptomatic). An RR greater than 1 indicates that the incidence rate of thyroid cancer is greater in the Fire Department compared with the Rochester Epidemiology Project, Rochester, Minnesota, and an RR less than 1 indicates that the incidence rate of thyroid cancer is greater in the Rochester Epidemiology Project.

Supplementary Content

eTable 1. Characteristics of WTC-exposed Fire Department rescue/recovery workers diagnosed with and without thyroid cancer from 09/12/2001 to 12/31/2018.

Variable	All Cases[a] (n=72)	Non-Cases (n=14,915)
WTC arrival group		
Morning of 9/11	13 (18.1)	2289 (15.4)
Afternoon of 9/11	32 (44.4)	6841 (45.9)
9/12/2001	12 (16.7)	2737 (18.4)
9/13/2001-9/24/2001	14 (19.4)	2606 (17.5)
After 9/24/2001	1 (1.4)	442 (3.0)
WTC work duration - months		
Median [IQR]	3.0 [1.0 – 6.0]	2.0 [1.0 - 5.0]
Sex		
Male	72 (100)	14,915 (100)
Age on 9/11		
Median [IQR]	38.9 [32.8 - 47.6]	40.0 [33.7 - 46.3]
Race		
White	64 (88.9)	13137 (88.1)
Nonwhite	8 (11.1)	1778 (11.9)
Current smoking status		
Never smoker	51 (70.8)	9132 (61.2)
Ever smoker	19 (26.4)	5514 (37.0)
Unknown	2 (2.8)	269 (1.8)
BMI at end of follow-up[b]		
Mean (SD)	30.6 (3.8)	30.4 (4.9)
Work assignment		
Firefighter	65 (90.3)	13178 (88.4)
Emergency medical service	7 (9.7)	1737 (11.7)
Deceased		
Yes	2 (2.8)	558 (3.7)
Age at diagnosis		
Median (IQR) [range]	50.0 (44.2, 58.2) [26.0, 76.3]	N/A
Years to diagnosis post-9/11		
Median [IQR]	11.5 [6.8 - 14.5]	N/A
Testing pre-diagnosis[c]		
Yes	38 (52.8)	N/A
Thyroid cancer histology		
Papillary	70 (97.2)	N/A
Follicular	2 (2.8)	N/A

Abbreviations: WTC=World Trade Center; BMI=Body Mass Index.
[a] Includes 7 cases in which no method of detection could be determined.
[b] BMI data only available for n=68 cases and n=14,579 non-cases.
[c] Includes chest computed tomography (CT), sinus CTs, sleep studies, gastrointestinal tests, echocardiograms, MRIs of the head and neck, stress tests, PET scans, cervical imaging, or surgery.



eFigure. Fire Department male thyroid cancer cases diagnosed per year by detection method, 2001-2018. Diagnosis years of confirmed Fire Department of the City of New York thyroid cancer cases, separated by asymptomatic, symptomatic, and unknown detect method categorizations.

eTable 2. Age-adjusted relative rates for secondary and sensitivity analyses.

Model	RR	95% CI
Secondary Analyses: World Trade Center Exposure		
Arrival at WTC site morning of 9/11	2.7	1.5-4.8
Arrival at WTC site afternoon of 9/11 or later	2.2	1.6-3.1
High Duration (≥3months WTC site)	2.4	1.6-3.6
Low Duration (<3 months at WTC site)	2.1	1.4-3.2
Arrival at WTC site morning of 9/11 and High Duration	2.8	1.3-6.1
Arrival at WTC site afternoon of 9/11 or later and Low Duration	2.3	1.6-3.1
Secondary Analysis: Primary analysis restricted to papillary thyroid cancer cases		
Overall	2.4	1.7-3.2
Early period[a]	2	1.2-3.3
Late period[b]	2.5	1.6-3.9
Asymptomatic	3.2	2.1-4.7
Symptomatic	0.9	0.5-1.7
Sensitivity Analysis: Primary analysis restricted to 30-79 years		
Overall	2.3	1.7-3.2
Early period[a]	1.8	1.1-3.0
Late period[b]	2.5	1.6-3.8
Asymptomatic	3.2	2.1-4.8
Symptomatic	1	0.5-1.8
Sensitivity Analysis: Primary analysis restricted to papillary thyroid cancer cases and 30-79 years		
Overall	2.4	1.7-3.3
Early period[a]	1.9	1.2-3.3
Late period[b]	2.5	1.6-3.9
Asymptomatic	3.2	2.2-4.8
Symptomatic	1.1	0.6-2.1

[a]9/12/2001-12/31/2009
[b]01/01/2010-12/31/2018

Specific Aim 3: To compare the risk of thyroid cancer among rescue/recovery workers in a medical monitoring program, the **WTC Health Program** (FDNY and General Responder Cohort (GRC)), to the risk among WTC-exposed rescue/recovery workers from **the World Trade Center Health Registry** ("the Registry") who are not also in either WTC Health Program. After comparing the overall risk, we will assess if the excess risk of thyroid cancer diagnosis among workers in the **WTC Health Program** compared with those in **the Registry** alone is limited to those who received CT scans as part of the increased medical surveillance in **WTC Health Program** cohorts and therefore due to incidental detection. *This aim will use data from the Joint Cancer Project (U01 OH011315) which is made up of the three main cohorts of WTC-exposed rescue/recovery workers; two cohorts, FDNY and the GRC are part of the **WTC Health Program** which offers on-site health care and medical surveillance including CT scans for respiratory conditions and the third cohort, **the Registry** is purely a research cohort without on-site access to health care or medical surveillance.*

Impact of healthcare services on thyroid cancer incidence among World Trade Center-exposed rescue and recovery workers

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1. Introduction

In recent decades, thyroid cancer incidence has increased at an annual rate of 3%, making it the 11th most common cancer in the United States and the 5th most common cancer among women.[1–4] Several studies have shown this increase to be limited to papillary carcinomas, a common and indolent histological form of thyroid cancer.[5–7] Rates of thyroid cancer mortality have also remained relatively low and stable at 0.5 per 100,000 persons, with a current 5-year relative survival rate of 98.3% (2010–2016).[8] The rising incidence, largely confined to the papillary histological subtype and early-stage tumors, coupled with consistently low mortality rates, has been suggested as evidence of thyroid cancer overdiagnosis.[9–14] Overdiagnosis may be fueled by the discovery of small, asymptomatic lesions resulting from diagnostic imaging, opportunistic screening, diagnostic cascade, and incidental findings.[9,12–14]

Elevated rates of thyroid cancer have been observed among rescue/recovery workers exposed to the September 11, 2001 (9/11) World Trade Center (WTC) disaster.[15–20] Many of these workers are enrolled in WTC medical monitoring and treatment programs (MMTPs) and are offered regular monitoring visits that provided screenings, diagnostic procedures, and treatments for WTC-certified conditions, at no-cost to the patient through the federally funded WTC Health Program, administered through the National Institute for Occupational Safety and Health

(NIOSH).[21] WTC MMTP examinations include computed tomography (CT) scans, when recommended by clinicians; how- ever, thyroid cancer ultrasonographic screenings are not provided unless a nodule is suspected on an examination or imaging paid for by the MMTP.
A recent study of WTC-exposed Fire Department of the City of New York (FDNY) firefighters and emergency medical service providers (EMS) enrolled in the WTC MMTP demonstrated that 81.5% of thyroid cancers were discovered among participants with asymptomatic tumors during routine medical monitoring examinations, which was three-fold higher than those diagnosed in the Rochester Epidemiology Project cohort.[22] A descriptive study which evaluated thyroid tumors among a subset of General Responder Cohort (GRC) rescue/recovery workers, who are also in the WTC MMTP, reported findings that surveillance bias could not be the sole contributor to the observed increased incidence because tumor sizes were similar to the comparison population.[17] The authors note, however, that most cases were diagnosed as a result of routine screening or unrelated medical care.
The current study seeks to build upon prior work by first comparing thyroid cancer incidence in WTC-exposed rescue/recovery workers enrolled in an MMTP and WTC-exposed rescue/recovery workers *not* enrolled in an MMTP to New York State (NYS) population rates; and second, by comparing rates among WTC-exposed rescue/recovery workers enrolled an MMTP to those not enrolled in an MMTP. We aim to describe whether secular trends affect the results and the potential magnitude of overdiagnosis that may be directly related to medical surveillance.

2. Methods

2.1 Overview of WTC Cohorts

The Combined WTC Rescue/Recovery Cohort (hereafter, Combined Cohort) used for this study consists of rescue/recovery workers from three WTC-exposed responder cohorts: the FDNY,[23] the GRC,[24] and the World Trade Center Health Registry (WTCHR).[25] Rescue/recovery workers include cleanup workers, construction and communication workers, EMS, firefighters, law enforcement, and volunteers. To ensure accurate case ascertainment and person-time calculations, the New York State Cancer Registry (NYSCR) resolved duplicates and discordant dates of enrollment, diagnosis, and death.[26] Additional details regarding the creation of the Combined Cohort, including de-duplication of subjects and data harmonization, are described elsewhere.[26] The Combined Cohort was classified into two groups: (1) WTC- exposed rescue/recovery workers enrolled in a New York-based WTC MMTP (MMTP rescue/recovery workers) and (2) WTC-exposed rescue/ recovery workers *not* enrolled in a New York-based WTC MMTP (non-MMTP rescue/recovery workers). MMTP rescue/recovery workers are enrolled in either the FDNY or the GRC cohort (some of whom were dually enrolled in the WTCHR) and receive medical monitoring exams or no-cost diagnostic/treatment services through the New York-based WTC MMTP. Non-MMTP rescue/recovery workers do not receive these ser- vices through a New York-based WTC MMTP.

2.2 Analysis Population

The source population included 69,102 rescue/recovery workers from the Combined Cohort. Individuals whose race or Hispanic ethnicity was unknown were excluded ($N = 5680$) due to the lack of a reliable comparison population. Participants younger than 18 years old on 9/11/2001 ($n = 165$) or who were missing year of birth ($n = 21$) were excluded, as were an additional 782 who enrolled in a responder cohort on or after the end of the study period (12/31/2015). The final study population consisted of 62,454 participants.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and was approved by Institutional Review Boards (IRBs) at Albert Einstein College of Medicine, New York City Department of Health and Mental Hygiene, the NYS Department of Health, and all 13 cancer registries. The Icahn School of Medicine at Mount Sinai and Stony Brook University IRB ruled the research exempt. Depending on the source cohort, participants provided informed consent, or their consent was waived.[26]

2.3 Outcome assessment

Incident cases of thyroid cancer were defined (using the Surveillance, Epidemiology, and End Results [SEER] site recode table [32010]) as ICD-O-3 topography code C73, and malignant behavior code 3. Cases were obtained by matching the Combined Cohort to data from the cancer registries of the following states: Arizona, California, Connecticut, Florida, Massachusetts, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Texas, Virginia, and Washington. Tumor characteristics such as diagnosis date, histology, and stage were also provided by state cancer registries. Cancer cases obtained from multiple states registries for the same participant were reconciled and de-duplicated by the NYSCR.[26] Histological codes were categorized as defined by Davies and Welch.[13]

2.4 Exposure measures and other covariates

The exposure of interest for our primary analysis was participation in a New York-based WTC MMTP. We used the first chest CT scan date within the follow-up period. Chest CT scan data were available for the entire follow-up period for FDNY participants and beginning in 2007 for all GRC participants, while there are no CT data available for non-MMTP rescue/recovery workers. We also evaluated arrival time at the WTC disaster site as a proxy for WTC exposure intensity.

This was included as a binary variable: arrived on 9/11 or arrived later. Demographic and other characteristics including age throughout follow-up, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian, Hispanic), death date, and smoking status provided by each cohort. We used the 15th of each month to calculate the age for participants missing day of birth. June 15th of the birth year was used for the 0.1% for whom both birth month and day were missing.

2.5 NYS comparison rates

Incident thyroid tumors in NYS were selected as the reference for our external analysis and were obtained and organized using SEER*Stat Software. Data were summarized in strata of persons and cases by 5-year-age-strata, race/ethnicity, sex, and calendar year (2002–2015).

2.6 Statistical methods

Demographic and other characteristics of the study population and thyroid cancer cases were assessed as counts/proportions and medians/interquartile ranges, as appropriate. Person-time accruals began on the later of 9/12/2001 or date of enrollment into a WTC rescue/recovery cohort. The follow-up period ended at the earlier of date of death or 12/31/2015. Rate ratios (RRs) were estimated using Poisson regression models, controlling for age group (5-year strata), race/ethnicity, sex, and calendar year. An advantage of using these models is that they allow the baseline hazard to change at numerous specified time intervals rather than at every event and they allow for incidence to be estimated in the reference group (i.e., change points). Change points were estimated using profile likelihood. Change point methodologies, which have been used in other WTC-related re- search,[27–29] are described in greater detail, elsewhere.[30–33] Briefly, the statistical model allows for a wide range of potential points in time at which the RRs may change, from early in the follow-up to late in the follow-up.

Thyroid cancer rates among MMTP and non-MMTP participants were assessed for all tumors (i.e., multiple primary), separately, overall and by sex, compared with NYS. Additionally, to evaluate the effect of augmented medical surveillance on incident thyroid cancer among MMTP participants, those who received a CT scan within the follow-up period and those who did not were compared with NYS, separately. We computed a population attributable fraction (i.e., the risk among MMTP rescue/recovery workers minus the risk among non-MMTP rescue/recovery workers) to further ascertain the absolute effect of medical monitoring on incident thyroid cancer among the Combined Cohort. We also illustrated adjusted thyroid cancer incidence rates trends during 2002–2015 for MMTP rescue/recovery workers, non-MMTP rescue/recovery workers, and NYS, respectively. For this analysis, we applied a locally weighted smoothing (LOESS) function for point estimates.

We conducted a secondary internal analysis to evaluate thyroid cancer that was diagnosed as the first primary cancers for an individual, using the non-MMTP rescue/recovery workers as the referent; therefore, all participants who had cancer before the start of follow-up or before enrollment in a WTC program were excluded (n = 1969). As in the primary analysis, rates were evaluated overall, and by sex.

A sensitivity analysis was conducted by repeating the primary and secondary analyses restricted to papillary thyroid carcinoma cases to assess the extent to which this subtype contributed to the overall models. To understand the association between WTC exposure and thyroid cancer incidence, two additional analyses were conducted. First, in an external analysis, data were restricted to only participants who arrived on the morning of 9/11 and were compared with NYS rates. The relative risk among MMTP rescue/recovery workers compared with non-MMTP rescue/recovery workers was also calculated. Second, in an internal analysis, rates among those who arrived on the morning of 9/11 were compared with those who arrived on 9/12 or later,

separately, for MMTP rescue/recovery workers and non-MMTP rescue/recovery workers. All analyses were performed using SAS (version 9.4; SAS Institute Inc.).

3. Results

3.1 WTC cohort characteristics

Characteristics of the final analytic cohort are presented in Table 1. The median age at the start of follow-up was 42.0 (interquartile range [IQR]: 36.0–49.0) and the median follow-up time was 11.7 years (IQR: 9.3–12.9). The cohort was predominantly non-Hispanic, White and male, and non-smokers. The majority of the Combined Cohort were MMTP rescue/recovery workers. Over 40% of the study population arrived at the WTC site on 9/11/2001. The MMTP rescue/recovery workers (N = 43,355) and non-MMTP rescue/recovery workers (N = 19,099) were similar in median age at the start of follow-up, median follow-up time, median body mass index (BMI), and smoking status at enrollment. The non-MMTP rescue/recovery workers had a lower proportion of males and a substantially lower proportion of participants who arrived at the WTC site the day of 9/ 11/2001 compared with MMTP rescue/recovery workers. Over half of the MMTP rescue/recovery workers were part of the GRC (62.7%), and a large majority (82.1%) did not receive a chest CT scan as part of a WTC MMTP before a thyroid cancer diagnosis or the end of follow-up.

Among the analytic cohort of 62,454 participants, there were 224 thyroid cancer patients with a total of 225 thyroid cancers. The majority (87.5%; N = 196) were first primary tumors and most (94.2%) were papillary tumors (Table 1). The median age at diagnosis was 49.3 (IQR: 42.4–55.4) and the median time to diagnosis after 9/11 was 9.6 years (IQR: 6.8–12.4). Among the 179 tumors in MMTP rescue/recovery workers, 44 (24.6%) had a chest CT scan before being diagnosed. Among all tumors, 148 (65.8%) were localized, 69 (30.7%) were regional, <5 (<3.5%) were distant, and <5 (<3.5%) had unknown staging. Similarly, among persons with a chest CT scan diagnosed with thyroid cancer, 28 (63.6%) tumors were localized and 14 (31.8%) were regional.

3.2 Evaluation the WTC-exposed combined cohort versus NYS

The crude rates for thyroid cancer incidence were 38.4 and 20.5 per 100,000 person-years for MMTP rescue/recovery workers and non-MMTP rescue/recovery workers, respectively, and 19.9 per 100,000 persons for the NYS population. Overall, the thyroid cancer incidence rate among MMTP rescue/recovery workers was twice that of the NYS population (RR: 2.31; 95% CI: 2.00–2.68) (Table 2, Model 1a). Among those who received a chest CT scan, the rate was even higher (RR: 2.84; 95% CI: 2.11–3.81) than the rate overall and the rate among those without a chest CT scan (Table 2, Model 2). The RRs comparing MMTP rescue/recovery workers to the NYS population were also significantly increased when stratified by sex, but the ratio was higher among males (RR for males: 2.46; 95% CI: 2.09–2.89 and RR for females: 1.94, 95% CI: 1.38–2.73) (Table 2, Models 1b,c). However, there was no difference in thyroid cancer incidence rate between non-MMTP rescue/recovery workers and the NYS population (RR: 0.96;

95% CI: 0.72–1.28); similar results were observed when stratified by sex. Rate ratios were consistently higher in sensitivity analyses when conducted only among papillary carcinomas. In the Combined Cohort, the population attributable fraction due to medical monitoring and treatment was 37.2%; that is, over one-third of thyroid cancers diagnosed could be attributed to medical monitoring as part of a New York-based WTC MMTP.

3.3 Change point analysis and adjusted incidence graphs

Adjusted incidence plots illustrated a consistently elevated risk of thyroid cancer among WTC MMTP participants throughout the study period compared with the NYS population, and rate differences become more pronounced beginning in 2011–2012 (Figure 1). However, we did not observe any significant change point using profile likelihood methods, as described above.

3.4 First primary cancer internal analysis: MMTP rescue/recovery workers versus non-MMTP rescue/ recovery workers

Thyroid cancer rates among the MMTP rescue/recovery workers were consistently elevated compared with non-MMTP rescue/recovery workers (Table 3). Overall, MMTP rescue/recovery workers had 2.66 times the risk of an incident thyroid cancer diagnosis compared with non-MMTP rescue/recovery workers during the follow-up period (95% CI: 1.82–3.88). The RR among females was slightly higher than among males (RR [female]: 2.84, 95% CI: 1.51–5.32; RR [male]: 2.45, 95% CI:1.53–3.93). The rate of thyroid cancer incidence among MMTP rescue/ recovery workers with a CT scan before the end of follow-up was over three times the rate of non-MMTP rescue/recovery workers (RR = 3.27; 95% CI = 2.05–5.23). Among those with no prior CT scan, the rate of thyroid cancer was 2.51 times higher than non-MMTP rescue/recovery workers (RR = 2.51; 95% CI = 1.70–3.70). Sensitivity analyses restricted to papillary tumors demonstrated similar results.

3.5 Evaluating WTC exposure intensity

Compared with NYS, MMTP rescue/recovery workers who arrived on 9/11 were over two times as likely (RR = 2.39; 95% CI = 1.93–2.96) and non-MMTP rescue/recovery workers who arrived on 9/11 were 1.78 times as likely (RR = 1.78; 95% CI = 1.03–3.07) to be diagnosed with thyroid cancer (Table 4). MMTP rescue/recovery workers had a mildly elevated risk relative to non-MMTP rescue/recovery workers (RR=1.34; 95% CI = 0.75–2.41). In an internal analysis that assessed arrival time at the WTC disaster site, we observed that MMTP rescue/recovery workers who arrived on 9/11 were not different from those who arrived on 9/12 or later (RR = 1.00; 95% CI = 0.75–1.35) and non-MMTP rescue/recovery workers who arrived on 9/11 were 2.34 times as likely to develop thyroid cancer (RR = 2.34; 95% CI = 1.21–4.52) compared with those who arrived later, after controlling for confounders.

4. Discussion

In this prospective cohort study of 62,454 WTC-exposed rescue/ recovery workers, we examined the effect of participation in a WTC MMTP in relation to a diagnosis of thyroid cancer. We found thyroid cancer rates among MMTP rescue/recovery workers were significantly elevated when compared with either non-MMTP res- cue/recovery workers or with the NYS population.

Further evidence that augmented medical surveillance is a large contributor to early thyroid cancer detection in the Combined Cohort is our finding that MMTP rescue/recovery workers who received a chest CT scan were slightly more likely to receive a diagnosis of thyroid cancer. Finally, results were similar when the outcome was restricted to papillary thyroid carcinomas, further supporting our hypothesis that less aggressive histological types were driving the study results.

We have previously compared the detection method of thyroid cancer cases (symptomatic or asymptomatic discovery) among FDNY WTC-exposed male firefighters enrolled in their WTC MMTP with a demographically similar cohort from Olmsted County, MN.[22] The overall age-adjusted incidence rate of thyroid cancer among the FDNY WTC-exposed cohort was significantly greater than in the reference population and was largely explained by the high rate of asymptomatic cancers detected among FDNY participants. While it is biologically plausible that carcinogens released following the WTC attacks partly contributed to the two- to three-fold greater risk of thyroid cancer among WTC-exposed persons relative to the general population,[18–20,23,34] results from the current study support earlier findings that elevated incidence rates are largely associated with incidental detection of small asymptomatic thyroid carcinomas.

Among FDNY WTC rescue/recovery workers, these tumors are often discovered via non-thyroid-related medical surveillance.[22] Therefore, the previously reported increased thyroid cancer rates among WTC-exposed cohorts[18–20,23] may represent heightened surveillance rather than a true increase in disease. The present analysis further examined this conclusion by using an expanded WTC-exposed population with access to medical monitoring (MMTP rescue/recovery workers) and without access (non-MMTP rescue/ recovery workers) to explore the role of surveillance and the extent of its influence on post-9/11 thyroid cancer incidence rates. The WTC MMTPs provide monitoring, diagnostic tests, and treatment, at no charge, for conditions specified by law and certified by NIOSH program administrators as WTC-related.

The differences found in thyroid cancer rates between MMTP rescue/recovery workers and non-MMTP rescue/recovery workers support our hypothesis that early and more frequent diagnoses of thyroid cancer in WTC MMTP enrollees were in large part due to increased medical surveillance.[35] While we observed that non- MMTP rescue/recovery workers who arrived at the disaster site earliest were at an increased risk of thyroid cancer, the risk among MMTP rescue/recovery workers of all exposure levels was even larger throughout follow-up, suggesting that surveillance may be driving this association more than dust exposure. Further, our adjusted incidence plot reveals a slight uptick beginning in 2012, the time period that coincides with increased use of chest CT due to expanded cancer coverage under the WTC MMTP.[21]

This study's findings are important because overdiagnosis of cancer often precedes unnecessary treatment, which can be costly and can contribute to harmful psychological consequences[7,36–39] as well as physical costs, such as surgical complications and risks of second cancers.[40,41] A high proportion of thyroid cancers in the study population were of the least aggressive subtype, and previous FDNY research found both little evidence of metastatic disease and continued low mortality rates[22]; thus, surgical excision and/or postsurgical ablation of thyroid remnants with

radio- active iodine may result in more harm than benefit, given the low risk of disease progression in many papillary thyroid cancers. We found that 37.2% of thyroid cancers diagnosed could be attributable to medical monitoring via a New York-based WTC MMTP; this represents the potential magnitude of the contribution of medical surveillance to thyroid cancer incidence among rescue/ recovery workers enrolled in a WTC MMTP and, the possible burden of unnecessary surgery. Currently, active surveillance of low-risk papillary thyroid cancers has been found to be a safe and accepted alternative to surgery for cancer management, without increased risk of recurrence or death.[42,43] This strategy would avoid surgical risk exposure and the need for subsequent thyroid replacement therapy. While active surveillance of small intrathyroidal cancers has the potential to circumvent surgical treatments and high rates of morbidity,[44,45] its adoption in the United States is in preliminary stages. Few studies have described the rate of papillary thyroid cancer growth under active surveil- lance, and it is unknown whether the favorable outcomes published recently are widely reproducible.[46,47]

Our approach to assess the influence of medical surveillance on WTC-related thyroid cancer incidence is not without limitations. First, we did not have information about years of employment or potentially important occupational exposures, which occurred before or after the WTC disaster and could insult the thyroid, endocrine, or metabolic systems. However, it is unlikely that this cohort was heavily exposed to other endocrine-related exposures, such as radiation, before or following the 9/11 disaster, as among these working populations, an elevated risk of thyroid cancer has not consistently been observed[48]; this is shown in our results as the rate of thyroid cancer at the start of follow-up was similar to the general population. Second, we were unable to ascertain potentially important socioeconomic confounders among each of the groups that may have contributed to increased surveillance irrespective of WTC MMTP cancer coverage. Among the non-MMTP rescue/recovery workers, we did not have information on other forms of insurance. Related to this point is that we did not have CT scan data for non-MMTP rescue/recovery workers. In addition, non-MMTP rescue/recovery workers may have not enrolled in a New York-based WTC MMTP for various reasons, including enrollment in the non-FDNY/ GRC federal WTC Nationwide Provider Network,[49] barriers related to the enrollment process, despite sustained efforts to inform them about the program, and not meeting eligibility requirements needed to enroll in a WTC MMTP.[50–52] As such, lack of data related to why they are not enrolled in a New York-based WTC MMTP, and chest CT data in non-MMTP rescue/recovery workers may have affected the observed findings. Finally, symptom data were not available for the Combined Cohort, so we were unable to assess the extent to which asymptomatic tumors contributed to the observed incidence. However, we note that in both the FDNY and GRC studies, the majority of tumors were diagnosed incidentally among asymptomatic patients.[17,22]

In our analysis evaluating high-intensity WTC exposure and thyroid cancer, using early arrival at the disaster site as a proxy, we observed an increased risk among non-MMTP rescue/recovery workers. It is plausible that this is partially a result of dust exposure, which was more ubiquitous early in the rescue/recovery effort. An alternate explanation is that this observation is a result of heightened surveillance relative to those with lower levels of WTC exposure which we were not able to control for in this study. Early arrival was not associated with thyroid cancer among

MMTP rescue/ recovery workers, potentially due to similar surveillance for all MMTP rescue/recovery workers. Some have suggested the rise in cases nationally may be caused, in part, by other risk factors such as atmospheric or medical radiation,[5,53] and by excess body mass.[5,53–56] However, among FDNY participants, thyroid cancer diagnoses were shortly after medical monitoring exams and BMI did not confound the relationship between surveillance and thyroid cancer in- cidence.[22,57] Finally, the Combined WTC Rescue/Recovery Cohort was likely a healthy working subset of the general population before WTC work and who resided mostly in the greater New York region, factors which may limit generalizability to less healthy participants in other regions of the country.

This study continues to increase our understanding of thyroid cancer incidence in WTC-exposed populations. In particular, our findings strongly support our hypothesis that enrollment in a medical monitoring program which includes screening and no-cost treatment benefits, facilitates increased diagnoses of occult asymptomatic lesions. Our results underscore the importance of evaluating the characteristics of healthcare systems when considering changes in the incidence rates of specific cancer diagnoses.

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Table 1. Selected demographic characteristics of analytic population

	Population (*N* = 62,454)	MMTP (*N* = 43,355)	Non-MMTP (*N* = 19,099)	Thyroid cancer cases[a] (*N* = 224)
Median age at 9/12/2001 (interquartile range [IQR])	42.0 (36.0–49.0)	42.0 (36.0–48.0)	43.0 (35.0–51.0)	42.0 (36.0–49.0)
Median follow-up time (years)	11.7 (9.3–12.9)	11.9 (8.2–14.3)	11.6 (11.4–11.9)	6.8 (3.5–9.5)
Median BMI (IQR)	29.2 (26.5–32.6)	29.7 (27.2–33.0)	28.3 (25.1–32.0)	30.5 (27.3–33.1)
Sex, *n* (%)[b]				
Males	52,707 (84.4)	38,846 (89.6)	13,861 (72.6)	171 (76.3)
Female	9,747 (15.6)	4,509 (10.4)	5,238 (27.4)	53 (23.7)
Race/ethnicity, *n* (%)[b]				
Non-Hispanic White	44,526 (71.3)	30,897 (71.3)	13,629 (71.4)	190 (84.8)
Non-Hispanic Black	6,019 (9.6)	3,904 (9.0)	2,115 (11.1)	11 (4.9)
Non-Hispanic American Indian	156 (0.3)	96 (0.2)	60 (0.3)	<5 (<1.8)
Non-Hispanic Asian/Pacific Islander	1168 (1.9)	521 (1.2)	647 (3.4)	<5 (<1.8)
Hispanic	10,585 (17.0)	7,937 (18.3)	2,648 (13.9)	19 (8.4)
Smoking status at enrollment, *n* (%)[b]				
Current	9,576 (15.3)	6,165 (14.2)	3,411 (17.9)	25 (11.2)
Former	14,705 (23.6)	9,582 (22.1)	5,123 (26.8)	49 (21.9)
Never	37,227 (59.6)	26,716 (61.6)	10,511 (55.0)	145 (64.7)
Unknown/missing	946 (1.5)	892 (2.1)	54 (0.3)	5 (2.2)
Initial arrival time to the WTC site, *n* (%)[b]				
9/11/2001	26,727 (42.8)	21,137 (48.8)	5,590 (29.3)	109 (48.7)
9/12/2001 to 06/30/2002	32,199 (51.6)	18,773 (43.3)	13,426 (70.3)	99 (44.2)
Unknown	3,528 (5.7)	3,445 (8.0)	83 (0.4)	16 (7.1)
Cohort membership, *n* (%)				
FDNY only	16,162 (25.8)	16,162 (37.3)	N/A	61 (27.2)
GRC	27,193 (43.5)	27,193 (62.7)	N/A	118 (52.7)
Registry only	19,099 (30.6)	N/A	19,099 (100.0)	45 (20.1)
CT scan before TC diagnosis or end of follow-up (12/31/2015), *n* (%)[b]				
MMTP with CT	7,743 (12.4)	7,743 (17.9)	N/A	44 (19.6)
MMTP without CT	35,612 (57.0)	35,612 (82.1)	N/A	135 (60.3)
Non-MMTP	19,099 (30.6)	N/A	19,099 (100.0)	45 (20.1)
Median age at diagnosis (IQR)	N/A	N/A	N/A	49.3 (42.4–55.4)

Median time to diagnosis since 9/12/ 2001 (IQR)	N/A	N/A	N/A	9.6 (6.8–12.4)
Histology, *n* (%)[b]				
Papillary	N/A	N/A	N/A	211 (94.2)
Follicular	N/A	N/A	N/A	10 (4.5)
Medullary	N/A	N/A	N/A	<5 (<1.0)
Anaplastic				0 (0.0)
Other	N/A	N/A	N/A	<5 (<1.0)

	Population (*N* = 62,454)	MMTP (*N* = 43,355)	Non-MMTP (*N* = 19,099)	Thyroid cancer cases[a] (*N* = 224)
First primary cancer, *n* (%)[b]				
Yes	N/A	N/A	N/A	196 (87.5)
No	N/A	N/A	N/A	28 (12.5)

Abbreviations: CT, computerized tomography; FDNY, Fire Department of the City of New York; GRC, General Responder Cohort; MMTP, Rescue/ recovery workers enrolled in a medical monitoring and treatment program; non-MMTP, rescue/recovery workers not enrolled in a medical monitoring and treatment program; Registry, World Trade Center Health Registry; TC, thyroid cancer.

[a]225 cancers among 224 participants. Participants could have more than one cancer.

[b]Percentages may not add up to 100 due to rounding.

TABLE 2 Thyroid cancer relative rates by WTC cohort using NYS as the referent group

	N cases	Person-years	RR	95% CI
Model 1a				
MMTP overall	180	469,269	2.31	2.00–2.68
Non-MMTP overall	45	219,446	0.96	0.72–1.28
NYS overall	46,855	235,913,263	Ref	
Model 1b				
MMTP males	147	424,276	2.46	2.09–2.89
Non-MMTP males	25	158,659	1.09	0.74–1.61
NYS males	11,461	112,624,375	Ref	
Model 1c				
MMTP females	33	44,993	1.94	1.38–2.73
Non-MMTP females	20	60,787	0.83	0.54–1.29
NYS females	35,394	123,288,888	Ref	
Model 2				
CT scan WTC-MMTP	44	95,205	2.84	2.11–3.81
No CT scan WTC-MMTP	136	374,064	2.18	1.84–2.58
Non-MMTP overall	45	219,446	0.96	0.72–1.28
NYS overall	46,855	235,913,263	Ref	

Note: Model 1a: Relative incidence comparing MMTP and non-MMTP rescue/recovery workers, separately to NYS rates. Model controls for race/ethnicity, sex, age, and calendar year. Model 1b: Relative incidence comparing male MMTP and non-MMTP rescue/recovery workers, separately to NYS rates. Model controls for race/ethnicity, age, and calendar year. Model 1c: Relative incidence comparing female MMTP and non-MMTP rescue/recovery workers, separately to NYS rates. Model controls for race/ethnicity, age, and calendar year. Model 2: Relative incidence comparing MMTP rescue/recovery workers, with CT scans, without CT scans, and non-MMTP rescue/recovery workers, separately to NYS rates. Model controls for race/ethnicity, sex, age, and calendar year.

Abbreviations: CI, confidence interval; MMTP, rescue/recovery workers enrolled in a Medical Monitoring and Treatment Program; non-MMTP, rescue/recovery workers not enrolled in a Medical Monitoring and Treatment Program; NYS, New York State; RR, rate ratio; WTC, World Trade Center.

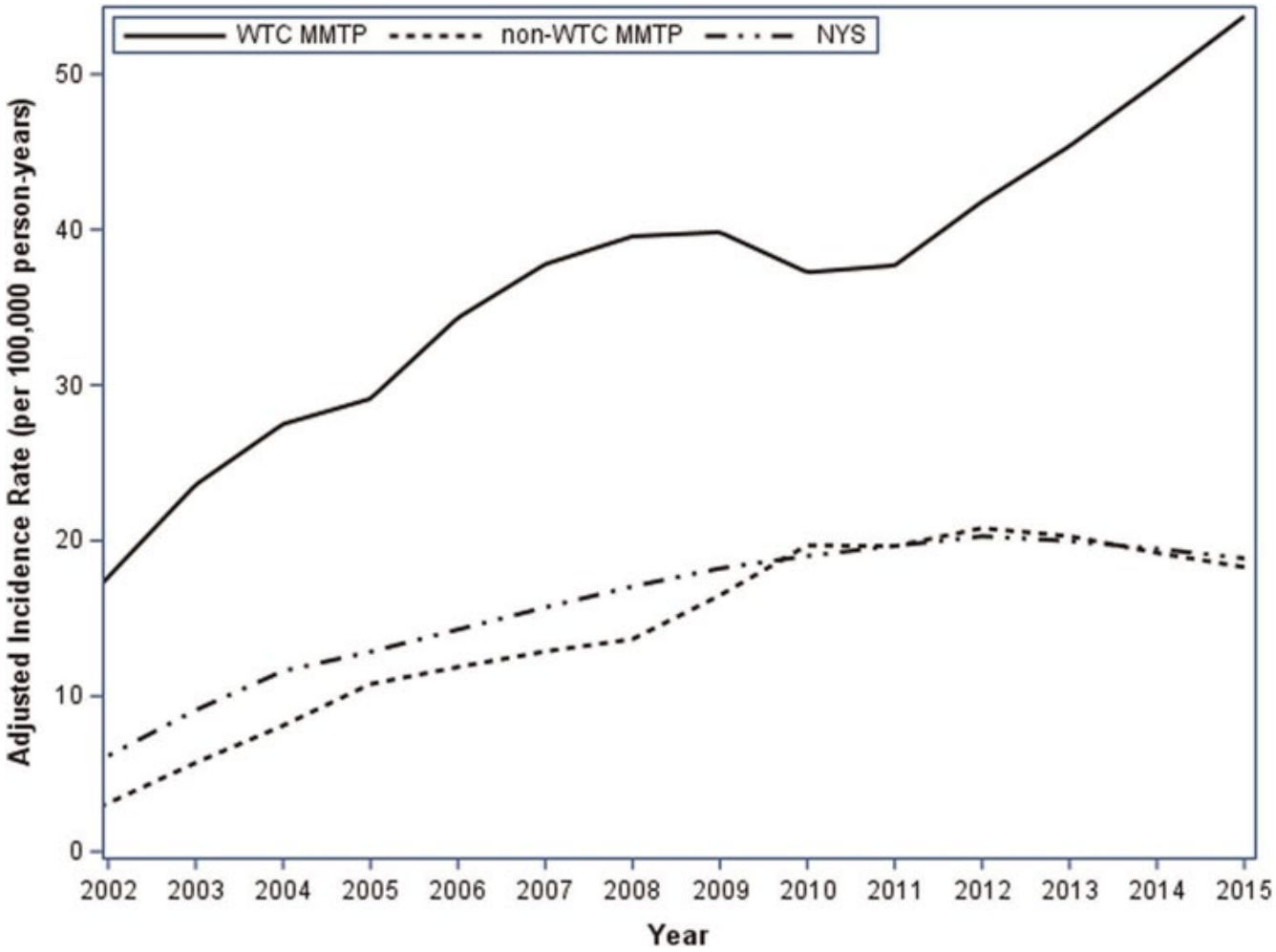

Figure 1. Adjusted thyroid incidence graph. Models are controlled for race/ethnicity, sex, and age throughout follow-up; rates are centered at non-Hispanic White race/ethnicity and ages 50–54; rates are displayed per 100,000 person-years; solid line: smoothed adjusted incidence curve for point estimates of each year of a World Trade Center (WTC) Combined Rescue/Recovery Cohort member who was enrolled in a medical monitoring and treatment program (MMTP); dashed line: smoothed adjusted incidence curve for point estimates for each year of a WTC Combined Rescue/Recovery Cohort member who was not enrolled in an MMTP (non-MMTP); mixed dashed and dotted lines: smoothed adjusted incidence curve for point estimates of each year using New York State population rates [Color figure can be viewed at wileyonlinelibrary.com]

Table 3. First primary thyroid cancer relative rates comparing MMTP rescue/recovery workers with non-MMTP rescue/recovery workers

	N cases	Person-years	RR	95% CI
Model 1a				
MMTP overall	159	458,511	2.66	1.82–3.88
Non-MMTP overall	37	214,894	Ref	
Model 1b				
MMTP males	130	414,618	2.45	1.53–3.93
Non-MMTP males	20	155,429	Ref	
Model 1c				
MMTP females	29	43,894	2.84	1.51–5.32
Non-MMTP females	17	59,465	Ref	
Model 2				
CT scan MMTP	40	93,251	3.27	2.05–5.23
No CT scan MMTP	119	365,261	2.51	1.70–3.70
Non-MMTP overall	37	214,894	Ref	
Model 3				
CT scan MMTP	40	93,251	1.34	0.93–1.94
No CT scan MMTP	119	365,261	Ref	

Note: Model 1a: Relative incidence comparing MMTP to non-MMTP rescue/recovery workers. Model controls for race/ethnicity, sex, age, and calendar year. Model 1b: Relative incidence comparing male MMTP to male non-MMTP rescue/recovery workers. Model controls for race/ethnicity, age, and calendar year. Model 1c: Relative incidence comparing female MMTP to female non-MMTP rescue/recovery workers. Model controls for race/ethnicity, age, and calendar year. Model 2: Relative incidence comparing MMTP rescue/recovery workers, with CT scans to non-MMTP rescue/recovery workers. Model controls for race/ethnicity, sex, age, and calendar year. Model 3: Relative incidence comparing MMTP rescue/recovery workers with CT scans to those without CT scans. Model controls for race/ethnicity, sex, age, and calendar year. Abbreviations: CI, confidence interval; MMTP, rescue/recovery workers enrolled in a Medical Monitoring and Treatment Program; non-MMTP, rescue/recovery workers not enrolled in a Medical Monitoring and Treatment Program; NYS, New York State; RR, rate ratio; WTC, World Trade Center.

Table 4. Thyroid cancer relative rates evaluating WTC exposure intensity

	N cases	Person-years	RR	95% CI
Model 1				
MMTP arrived on 9/11	84	221,027	2.39	1.93–2.96
Non-MMTP arrived on 9/11	13	40,103	1.78	1.03–3.07
NYS	46,855	235,913,263	Ref	
Model 2				
MMTP arrived on 9/11	84	221,027	1.00	0.75–1.35
MMTP arrived on 9/12 or later	96	248,242	Ref	
Model 3				
Non-MMTP arrived on 9/11	13	40,103	2.34	1.21–4.52
Non-MMTP arrived on 9/12 or later	32	179,343	Ref	

Note: Model 1: Relative incidence of multiple primary thyroid cancer comparing MMTP and non-MMTP rescue/recovery workers that first arrived at the WTC on 9/11, separately, to NYS rates. Model controls for race/ethnicity, sex, age, and calendar year. Model 2: Relative incidence of multiple primary thyroid cancer comparing MMTP participants that first arrived at the WTC on 9/11, to MMTP participants who arrived on 9/12 or later. Model controls for race/ethnicity, sex, age, and calendar year. Model 3: Relative incidence of multiple primary thyroid cancer comparing non-MMTP participants that first arrived at the WTC on 9/11, to non- MMTP participants who arrived on 9/12 or later. Model controls for race/ethnicity, sex, age, and calendar year.

Abbreviations: CI, confidence interval; MMTP, rescue/recovery workers enrolled in a Medical Monitoring and Treatment Program; non-MMTP, rescue/recovery workers not enrolled in a Medical Monitoring and Treatment Program; NYS, New York State; RR, rate ratio; WTC, World Trade Center.

Publications

Journal Articles:

Colbeth HL, Genere, N: [2020] Evaluation of Medical Surveillance and Incidence of Post-September 11, 2001, Thyroid Cancer in World Trade Center-Exposed Firefighters and Emergency Medical Service Workers. JAMA Internal Medicine, 180(6):888-895.

Goldfarb DG, Colbeth HL: [2021] Impact of healthcare services on thyroid cancer incidence among World Trade Center-exposed rescue and recovery workers. American journal of industrial medicine, 10.1002/ajim.23277.

Conference Abstracts:

Colbeth HL, Jaber, N: [2019] Detection and Incidence of Thyroid Cancer among Three Cohorts of WTC-Exposed Rescue and Recovery Workers. New York City Epidemiology Forum 6th Annual Conference, New York, New York, February 2019

Colbeth HL, Genere, N: [2019] Mechanism Of Detection Of Thyroid Cancer Among World Trade Center Exposed Rescue And Recovery Workers. Society for Epidemiological Research, 52nd annual meeting, Minneapolis, Minnesota, June 18-21, 2019.

Notes:

Cumulative Inclusion Enrollment Table

Comments: "Native Hawaiian or Other Pacific Islander" was included in the category of "Asian" for some of the participants so was categorized as "Asian/Native Hawaiian or Other Pacific Islander"

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/ Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	19	138								157
Asian	281	904								1185
Native Hawaiian or Other Pacific Islander										0
Black or African American	1517	4529								6046
White	5587	39255								44842
More than One Race										0
Unknown or Not Reported				2453	8213		859	5326		16851
Total	7404	44826	0	2453	8213	0	859	5326	0	69081

Inclusion of gender and minority study subjects
There were no exclusions made on the bases of gender or minority status.

Inclusion of Children
No children were included in this study as all rescue/recovery workers were at least 18 years old on 9/11/2001.

Materials available for other investigators
Digital data are available for other investigators upon reasonable request and approval of all parties.