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Abstract

Background: A recent study of World Trade Center (WTC)-exposed firefighters and emergency medical service workers demonstrated that elevated thyroid cancer incidence may be attributable to frequent medical testing, resulting in the identification of asymptomatic tumors. We expand on that study by comparing the incidence of thyroid cancer among three groups: WTC-exposed rescue/recovery workers enrolled in a New York State (NYS) WTC-medical monitoring and treatment program (MMTP); WTC-exposed rescue/recovery workers not enrolled in an MMTP (non-MMTP); and the NYS population.

Methods: Person-time began on 9/12/2001 or at enrollment in a WTC cohort and ended at death or on 12/31/2015. Cancer data were obtained through linkages with 13 state cancer registries. We used Poisson regression to estimate rate ratios (RRs) and 95% confidence intervals (CIs) for MMTP and non-MMTP participants. 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: The thyroid cancer incidence rate among MMTP participants was more than twice that of NYS population rates (RR = 2.31; 95% CI = 2.00–2.68). Non-MMTP 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.

Conclusion: Our findings support the hypothesis that no-cost screening (a benefit provided by WTC-MMTPs) is associated with elevated identification of thyroid

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Funding information

Centers for Disease Control and Prevention, Grant/Award Number: 6NU58DP006309; Agency for Toxic Substances and Disease Registry, Grant/Award Number: U50/ATU272750; National Cancer Institute, Grant/Award Numbers: 75N91018D00005 (Task Order 75N91018F00001), P30 CA013330; National Institute for Occupational Safety and Health, Grant/Award Numbers: 200-2011-39378, 200-2011-39383; 200-2017-93325, 200-2017-93326, U01 OH011480, U01 OH011681, U01 OH011931, U01 OH011932, U01OH011315, U50/OH009739

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.

KEYWORDS

longitudinal cohort, occupational epidemiology, surveillance, thyroid cancer, World Trade Center

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; however, 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 services 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

research,^{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 | Evaluating 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.

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)

(Continues)

TABLE 1 (Continued)

	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.

^a225 cancers among 224 participants.

Participants could have more than one cancer.

^bPercentages may not add up to 100 due to rounding.

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 rescue/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

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.

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 rates²²; thus, surgical excision and/or postsurgical ablation of thyroid remnants with radioactive 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 surveillance, 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

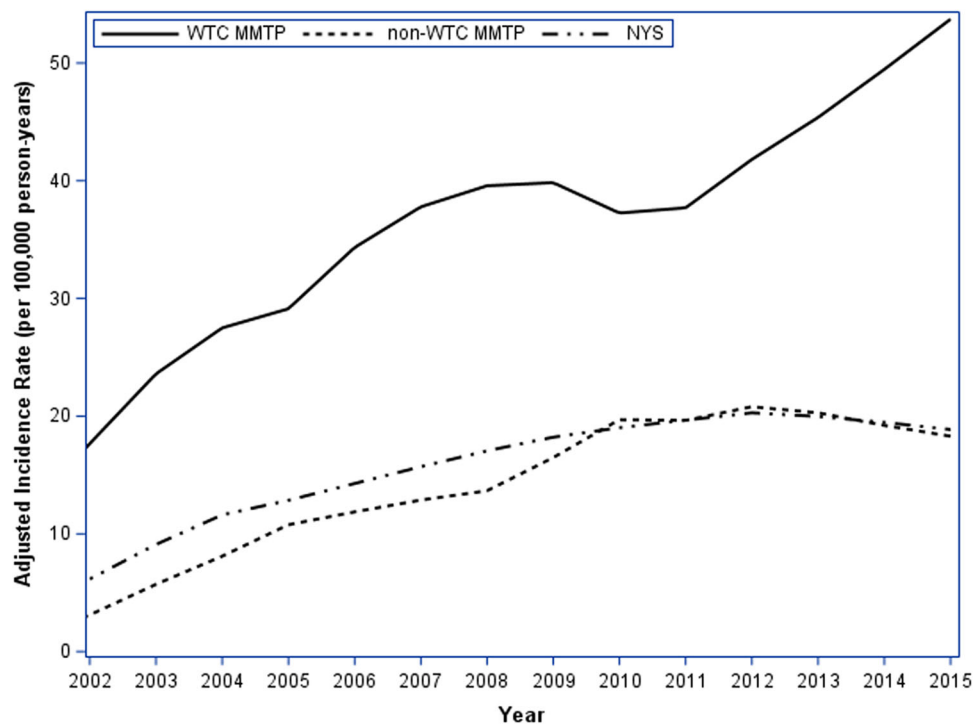


FIGURE 1 Adjusted thyroid incidence graph. Models are controlled for race/ethnicity, sex, and age throughout follow-up; rates are centered at non-Hispanic White race/ethnicity and ages 50–54; rates are displayed per 100,000 person-years; solid line: smoothed adjusted incidence curve for point estimates 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

consistently been observed⁴⁸; 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 incidence.^{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

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.

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.

ACKNOWLEDGMENTS

We thank the 13 state cancer registries for providing record linkages: Bureau of Cancer Epidemiology, New York State Department of Health (DOH); Arizona Cancer Registry Department of Health Services (DOHS); California Cancer Registry, Department of Public Health (DPH); Connecticut Tumor Registry,

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.

Connecticut DPH; Florida Cancer Registry, Florida DOH; Massachusetts Cancer Registry, Massachusetts DPH; New Jersey State Cancer Registry, New Jersey DOH and Rutgers Cancer Institute of New Jersey; North Carolina Central Cancer Registry, State Center for Health Statistics; Ohio Cancer Incidence Surveillance System, Ohio DOH; Bureau of Health Statistics and Research, Pennsylvania DOH; Texas Cancer Registry, Texas Department of State Health Services, Virginia Cancer Registry, Virginia DOH, and Washington State Cancer Registry, Washington DOH. This study was supported through the National Institute for Occupational Safety and Health (NIOSH) cooperative agreements (U01 OH011681, U01 OH011931, U01OH011315, U01 OH011932, U01 OH011480, and U50/OH009739) and contracts (200-2011-39378, 200-2011-39383, 200-2017-93325, and 200-2017-93326). Additionally, this study was supported cooperative agreement 6NU58DP006309 awarded to the New York State Department of Health by the Centers

for Disease Control and Prevention (CDC) and by Contract 75N91018D00005 (Task Order: 75N91018F00001) from the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services. This study was also supported by cooperative agreement U50/ATU272750 from the Agency for Toxic Substances and Disease Registry (ATSDR), CDC, which included support from the National Center for Environmental Health, CDC; and by the New York City Department of Health and Mental Hygiene (NYC DOHMH). This study was also supported by grant P30 CA013330 from the National Cancer Institute (NCI), NIH.

Additional Acknowledgments and Disclaimers from Individual State Cancer Registries: The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN26120180009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors. The Connecticut Department of Public Health Human Investigations Committee approved this research project, which used data obtained from the Connecticut Department of Public Health. The Connecticut Department of Public Health does not endorse or assume any responsibility for any analyses, interpretations or conclusions based on the data. The authors assume full responsibility for all such analyses, interpretations, and conclusions. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDS), the statewide cancer registry funded by the Florida Department of Health (DOH), and the Centers for Disease Control and Prevention's National Program of Cancer Registries (CDC-NPCR). The views expressed herein are solely those of the author(s) and do not necessarily reflect those of the DOH or CDC-NPCR. Cancer incidence data used in these analyses were obtained from the Ohio Cancer Incidence Surveillance System (OCISS), Ohio Department of Health (ODH), a cancer registry partially supported by the National Program of Cancer Registries at the Centers for Disease Control and Prevention (CDC) through cooperative agreement Number NU58DP006284. The use of these data does not imply that ODH or CDC agrees or disagrees with the analyses, interpretations, or conclusions in this report (or publication/presentation). These data were supplied by the Bureau of Health Statistics & Registries, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

Rachel Zeig-Owens, Charles B. Hall, and Paolo Boffetta participated in the conception, design of the work, and the acquisition and/or methodology of the funding for the work. David G. Goldfarb, Hilary L. Colbeth, Christopher R. Dasaro, Andrew C. Todd, Jiehui Li, Janette Yung, Amy R. Kahn, and Baozhen Qiao participated in data curation. David G. Goldfarb, Hilary L. Colbeth, Molly Skerker, and Rachel Zeig-Owens conducted analyses and interpretation of data for the work. Drafting the work or revising it critically for important intellectual content was done by David G. Goldfarb, Hilary L. Colbeth, Charles B. Hall, Paolo Boffetta, and Rachel Zeig-Owens. All authors provided the final approval of the version to be published. Rachel Zeig-Owens agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Data that support the findings of the study may be obtained from the corresponding author (Rachel Zeig-Owens) upon reasonable request after approval by the Steering Committee for the Combined Cohort in accordance with the official Data Sharing Plan.

ETHICS APPROVAL AND INFORMED CONSENT

This study was approved by Institutional Review Boards (IRBs) at Albert Einstein College of Medicine, New York City Department of Health and Mental Hygiene, the New York State 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.

DISCLAIMER

The funders of the study had no role in the design of the study, data linkage activities, analysis, interpretation, writing of the manuscript, nor in the decision to publish the results. The authors have no disclosures. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention–National Institute for Occupational Safety and Health.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Goldfarb DG, Colbeth HL, Skerker M, et al. Impact of healthcare services on thyroid cancer incidence among World Trade Center-exposed rescue and recovery workers. *Am J Ind Med.* 2021;64:861-872. <https://doi.org/10.1002/ajim.23277>