A. OVERALL COVER PAGE

Project Title: Thyroid cancer risk in WTC responders	
Grant Number: 5U01OH010984-03	**Project/Grant Period:** 09/01/2016 - 08/31/2019
Reporting Period: 09/01/2018 - 08/31/2019	**Requested Budget Period:** 09/01/2018 - 08/31/2019
Report Term Frequency: Annual	**Date Submitted:** 12/01/2020
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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The objectives of this project were to elucidate the reasons for the increased incidence of thyroid cancer among WTCHP participants, and to explore the behavior of these cancers. This project investigated whether thyroid cancers among WTCHP participants differed from a clinical, epidemiologic and molecular viewpoint from thyroid cancers in WTC-unrelated patients.

The specific aims of the project were:

Aim 1. To analyze if thyroid cancer over-diagnosis occurred among WTCHP because of increased surveillance. We compared clinical characteristics of thyroid cancer tumors diagnosed within WTCHP with those characteristics of a group of thyroid cancers who are WTC- unrelated, frequency matched by gender and race. The hypotheses were that over-diagnosis due to screening will result in a large number of early stages thyroid cancers among WTCHP. Tumor clinical characteristics (tumor stage, size, nodal involvement, local and distant metastatic spread), distribution of classic thyroid cancer risk factors, and medical history (frequency of medical visits and of chest imaging, diagnosis because of symptoms vs. asymptomatic finding during medical surveillance) were compared between WTC and non-WTC cases. This helped dissect whether excess cancer incidence reflects a real increase in risk or is due to over-diagnosis from medical surveillance.
Aim 2. To test if over-diagnosis of malignant thyroid cancer occurred among WTCHP responders. A panel of molecular markers that distinguish benign from malignant carcinoma was tested in archived thyroid cancer tissue from WTC responders and non WTC related thyroid cancers. The expression of 4 genes (DDIT3, PVALB, ITM1, and C1orf24), which were found to be able to accurately discriminate between benign and malignant thyroid follicular, papillary and Hurtle cell carcinoma were tested as a standard to eliminate false positives for the diagnosis of malignancy. Currently there is uncertainty in scoring a thyroid cancer as malignant based on histopathology alone. We hypothesized that a false diagnosis of malignancy was more likely to occur among WTC responders than in non WTC thyroid cancers, because of increased surveillance and a more conservative approach towards this population.

This project represents the first in-depth epidemiologic and molecular analysis of thyroid cancer excess among WTC rescue and recovery workers. The results have important implications in terms of surveillance and care and important implications on the surveillance and clinical management of thyroid cancer, a frequent cancer among WTCHP members. It also represents the first step to a more extensive study involving cases from the other two WTC exposed cohorts, where thyroid cancer is also shown to have a statistically significant increase.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

The results of this project were published on peer-reviewed scientific journals, which have high diffusion. The results were presented to responders and stake holders at the World Trade Center meetings. Including the annual memorial for families and victims of 9/11.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

October 30, 2020

The Final Progress Report

Title: Thyroid Cancer Risk in WTC Responders

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Grant Award Number: PAR16-098 U01 OH010984

Project Start- End Dates: 9/1/2016 – 8/31/2020

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List of Abbreviations

Body Mass Index	BMI
Conventional PTC	CPTC
Deoxyribonucleic acid	DNA
Fine-needle aspiration	FNA
Follicular thyroid adenoma	FTA
Follicular variant papillary thyroid carcinoma	FVPTC
Hürthle cell adenoma	HCA
Hürthle cell carcinoma	HCC
International Agency for Research on Cancer	IARC
New York City	NYC
Odds ratio	OR
Papillary thyroid cancer	PTC
Polycyclic aromatic hydrocarbons	PAHs
Represent hyperplasia	HN
Standardized incidence ratio	SIR
Surveillance, Epidemiology, and End Results	SEER
Volatile Organic compounds	VOCs
World Trade Center	WTC
World Trade Center Health Program	WTCHP

Title: Thyroid Cancer Risk in WTC Responders

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Abstract

A statistically significant excess of thyroid cancer has been identified among World Trade Center (WTC) rescue and recovery workers included in the WTC Health Program (WTCHP) at Mount Sinai in New York. Similar results have also been reported in two other cohorts, the WTC-exposed firefighters and the NYC Department of Health exposed residents. Heightened diagnosis due to increased medical surveillance is a possible explanation for greater than expected numbers of thyroid cancer diagnoses.

The objectives of this project were to elucidate the reasons for the increased incidence of thyroid cancer among WTCHP participants, and to explore the behavior of these cancers. This project investigated whether thyroid cancers among WTCHP participants differ from a clinical, epidemiologic and molecular viewpoint from thyroid cancers in WTC-unrelated patients, with the following specific aims: 1) analyze if thyroid cancer over-diagnosis occurred among WTCHP responders because of increased surveillance and 2) test if over-diagnosis of malignant thyroid cancer occurred among WTCHP responders

For aim 1, thyroid cancer WTC patients were compared with 949 non-WTC thyroid cancer cases identified within the Mount Sinai cancer registry. No significant difference in tumor size ($p= 0.405$) and age at diagnosis ($p=0.225$) was found between the two groups, suggesting that surveillance bias does not adequately explain the excess thyroid cancer risk alone.

For aim 2, 30 patients with available thyroid tumor tissue samples were matched with 30 non-WTC thyroid cancer patients on age, sex, and histology and were evaluated using established cancer-detection four-biomarker panel of malignancy to determine the false positive rate for malignancy. All samples tested were confirmed to be malignant, suggesting that over-diagnosis by virtue of misdiagnosis of a benign tumor as malignant does not explain the increased incidence of thyroid cancer observed in WTC responders. Rather, there may be an increased incidence of thyroid cancers by virtue of WTC disaster exposure and thus increased screening may be justified in this population.

Our results suggest that screening of WTC responders, at least in the case of thyroid cancer, may be beneficial as it might be that the yearly screening visits by the WTCHP are identifying true cases of thyroid cancer earlier, increasing the possibility of a favorable prognosis. Furthermore, future studies should investigate a causal link between thyroid cancer in WTC responders and exposure to potentially thyroid carcinogenic agents at Ground Zero as well as the potential of more aggressive thyroid cancer in the WTC dust exposed population.

Section 1

Significant or Key Findings

The primary aim of the study was to analyze whether thyroid cancer over-diagnosis occurred among WTC participants due to increased surveillance. We therefore compared demographic and clinical characteristics of WTC thyroid cancer tumors with non WTC-exposed thyroid cancers. We found that WTCHP thyroid cancer tumors were of a similar size at diagnosis and were diagnosed at a similar age compared to a cohort of thyroid cancer cases treated at Mount Sinai without WTC exposure. These results do not support the surveillance bias hypothesis, under which expected to have smaller tumors diagnosed at earlier ages in the WTC group.

Our secondary aim was to evaluate whether over-diagnosis of malignant thyroid cancer may be occurring among WTC responders due to physician bias resulting in false-positive cancer diagnoses**.** We therefore evaluated a highly accurate panel of thyroid cancer specific molecular markers, including DDIT3, ITM1, C1orf24, PVALB antibodies, in archived thyroid cancer tissue from WTC and non-WTC thyroid cancers. This panel permits to accurately discriminate benign from malignant thyroid carcinoma. All thyroid tumor samples from the two groups and histology types tested positive for malignancy using the panel of molecular markers, indicating no false positive cancer diagnosis. This suggests that over-diagnosis by virtue of misdiagnosis of a benign tumor as malignant does not explain the excess thyroid cancer risk in the WTC cohort.

Translation of Findings

The results of our study suggest that 1) surveillance bias may play a role, but does not solely explain the excess risk of thyroid cancer in WTC responders and 2) physician bias resulting in a false-positive thyroid cancer diagnosis does not explain increased thyroid cancer incidence in the WTC population. We were able to confirm through molecular markers, that during the yearly screening visits, true cases of thyroid cancer were identified.

Although the mechanism between WTC dust exposure and thyroid cancer remains unclear, the possibility of identifying true thyroid cancer earlier, potentially at a less advanced stage in the WTC-exposed population may warrant screening of recovery and rescue workers, New York fire fighters and other WTC exposed populations.

Research Outcomes/Impact

Our project presents important implications on the surveillance and clinical management of thyroid cancer, a frequent cancer among WTCHP members, by showing that increased surveillance is warranted. It also represents the first step to a more extensive study involving cases from the other two WTC exposed cohorts, where thyroid cancer is also shown to have a statistically significant increase.

Disentangling the effect of WTC-related exposures on clinical cancer characteristics and incidence is a particularly important aspect in thyroid cancer. Excess diagnoses of a thyroid malignancy may lead to excess head and neck surgery via thyroidectomy, an approach that carries a sizable risk of complications. Patients may also require supplemental life-long replacement therapy in tandem.

Testing thyroid samples with the proposed set of antibodies biomarkers may become the recommended clinical practice to be added to the diagnostic tools for thyroid cancer, especially within the WTC first responder population, and could be recommended to improve the diagnostic accuracy of suspicious thyroid nodules from both tissue sections and FNA samples.

These results will also bear other important implications. They will address anxiety in the interpretation of the results produced so far, and will guide future surveillance of WTCHP members with respect to thyroid cancer. The implications of the results will go beyond the WTC populations, as they will provide unique and novel information on thyroid over-diagnosis due to surveillance in the US general population.

Section 2

Scientific Report

Background

An increased risk of thyroid cancer has been reported in the Mount Sinai World Trade Center (WTC) responders. Similar results have also been reported in two other cohorts, the WTC-exposed firefighters and the NYC Department of Health exposed residents [Zeig-Owens et al., 2011; Jordan et al., 2011]. The excess risk is in the range of 2-3 times the incidence reported by the Cancer Registries.

It is unclear whether the excess is associated with WTC-related exposures or represents an artifact. There are several possible explanations for an increase in thyroid cancer incidence, and the ability to disentangle the roles of the various contributors would have major clinical and preventive consequences. One possibility is an over-diagnosis of thyroid cancer cases due to enhanced surveillance (surveillance bias), and evidence for this phenomenon would represent an important reassuring message to WTC responders and workers.

On the other hand, if thyroid cancer clinical and molecular characteristics support a specific carcinogenic effect of WTC exposures on the thyroid, that would argue for implementing specific screening activities among the exposed cohorts, with the intent of early detection and early treatment.

CHARACTERISTICS	N (%)
Sex	
Male	17,781 (85)
Female	3,203 (15)
Median age on 9/11 (years)	38
Age on 9/11 (years)	
< 40	11,835 (56)
> 40	9,149 (44)
Race/ethnicity	
Black	2,688 (13)
White non-Hispanic	12,337 (59)
White Hispanic	1,345 (6)
Hispanic missing race	3,996 (19)
Other	553 (3)
Missing	155 (1)
Smoking history	
current	3,374 (16)
former	5,054 (24)
never	12,240 (58)
missing	316 (2)

Table 1 – Description of the WTC research cohort

The WTCHP Responders who participated as rescue, recovery, and cleanup efforts at the WTC sites have been enrolled at Mount Sinai in the World Trade Center Health Program (WTCHP), which is funded under the James Zadroga 9/11 Health and Compensation Act of 2010, on the basis of eligibility criteria including type of duties, site location, and dates and hours worked. The medical protocol for the monitoring program includes self- administered physical and mental health questionnaires, as well as a physical examination, laboratory tests, spirometry, and a chest radiograph. Over 27,000 responders have had a least one monitoring visit in the WTCHP and have consented to aggregation of their data. A total of 20,984 responders have consented to have their records used for medical research (Table 1). Over one third of WTCHP members belong to minority groups; policemen and other protective service workers represent the largest occupational group. One important characteristic is the high proportion of never smokers; about 20% experienced high or very high WTC-related exposure, as defined in previous studies.

Increased incidence of thyroid cancer among WTC responders: In the first analysis of cancer incidence of subjects included in the WTCHP cohort, 26 cases of thyroid cancer occurred at least six months after enrollment. The corresponding figure of expected cases was 8.3, resulting in a standardized incidence ratio (SIR) of 3.12 (95% CI: 2.04 to 4.57). The study follow-up was completed at the end of 2008; the current follow-up was extended to 2012, and has significantly increased the sample size to 148 cases, Results on thyroid cancer (Table 2) were also reported for a separate cohort of NY firefighters, where 17 cases were observed among exposed firefighters (SIR: 3.07; 95% CI: 1.86 to 5.08) [Zeig-Owens et al., 2011], and among the NYC Department of Health exposed residents, where 13 cases of thyroid cancers were reported (SIR: 2.02; 95% CI: 1.07 to 3.45). **These results, derived from partially overlapping cohorts comprised of both workers and residents, suggest that WTC responders experienced a 2 to 3 fold increased incidence of thyroid cancer.** The data available so far do not allow distinguishing the possible contribution of WTC exposures from other potential causes of increased incidence.

Table 2- excess risk of cancer in WTC populations

Cancer site	N	FDNY (PY=61,884)	N	WTCHR (PY=41,280)	N	WTCHP (PY=153,077)
All sites	263	1.10 (0.98 -1.25)	223	1.14 (0.99 -1.30)	302	1.06 (0.94 - 1.18)
Thyroid	17	**3.07 (1.86 -5.08)**	13	**2.02 (1.07 - 3.45)**	26	**3.12 (2.04 - 4.57)**

WTC-related exposures and thyroid cancer: The WTC attacks resulted in exposure to several known and suspected human carcinogens, including soot, benzene, and other volatile organic compounds (VOCs) from jet fuels, as well as WTC dust and smoke. The dust contained asbestos, silica, cement dust, glass fibers, heavy metals, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, and polychlorinated dibenzofurans and dioxins from the burning and collapse of the planes and the tower. Most of these agents have no known carcinogenic mechanism on the thyroid; thyroid cancer has been associated to exposure to iodine-131, but there is no evidence that this radionuclide was present at Ground Zero. The only possible general carcinogenetic effects that could have occurred in the thyroid are both early (DNA damage, mutation, reduced DNA repair), as well as late events (cell proliferation, chronic inflammation). WTC exposures might act on cancer risk through other mechanisms such as reduced immunological competence and epigenetic alterations of gene regulation, although there is no precedent or direct evidence supporting either of these mechanisms as being involved in thyroid cancer.

Epidemiology and natural history of thyroid cancer: The age adjusted incidence of thyroid cancer in the US was 12.9 per 100,000 during the period 2007-2011, accounting for 4% of all newly diagnosed cancer cases (SEER facts sheet: http://seer.cancer.gov/statfacts/html/thyro.html), and making it the 9th most common cancer in the US. Median age at diagnosis is 50 years, with 35% of cases being diagnosed in persons below the age of 45 years. The cancer disproportionately affects females, with a ratio female to male of 3 to 1. Rates for new thyroid cancer cases have been rising on average 5.5% each year over the last 10 years. Thyroid cancer mortality is low, but is highest among people aged 75-84; the SEER data base reports a 5-year survival of 98%; death rates have been rising on average 0.8% each year over 2002-2011.

Thyroid cancer over diagnosis: A diagnosis of thyroid cancer is usually determined based on symptoms, or due to an incidental finding during monitoring visits that involve chest computed tomography scans and/or ultrasounds. It has been reported that at least one third of adults harbor small papillary thyroid cancers, the vast majority of which will not produce symptoms during a person's lifetime, while an estimated 4% to 7% of the adult population develops clinically palpable thyroid nodules during their lifetime. With the advent of ultrasound in medical practice, an increasing

number of impalpable thyroid nodules can be detected in the general population; the proportion of people with these nodules is estimated to be as high as 20-67%. A recent article [Ahn et al, 2014] reports dramatic increase in the rates of differentiated thyroid cancer with stable mortality rates (a combination that usually suggests over-diagnosis) in South Korea, following the introduction of routine thyroid imaging screening in the universal healthcare system. Similarly increasing rates of thyroid-cancer detection have been documented in France, Italy, Croatia, the Czech Republic, Israel, China, Australia, Canada, and the US (Cancer in Five Continents, IARC, France).
Chest imaging is known to increase detection of incidental thyroid nodules and WTC responders with respiratory health problems are likely to have been referred for imaging at higher rates, thus increasing the chance discovery of a thyroid nodule.

Histological types: Well-differentiated thyroid cancer histology includes papillary and follicular types. Papillary thyroid cancer (PTC) is the most frequent type of thyroid malignancy. Although neck lymph node metastasis at diagnosis was reported in nearly 35% of the cases, distant metastases from PTC may occur with a frequency ranging from 1.7-8.4% in most studies. Three major PTC variants of PTC have been reported: conventional PTC (CPTC), follicular-variant PTC (FVPTC) and tall-cell variant. Mortality associated with tall-cell PTC was significantly higher than that associated with CPTC and FVPTC. Follicular thyroid carcinoma (FTC) is the second most common thyroid cancer, comprising 15% of all thyroid cancers, and is considered more aggressive than PTC. Vascular invasion is a characteristic of FTC, and therefore distant metastasis is more common.

Diagnostic markers of thyroid cancer: The first step in the evaluation of a thyroid nodule is cytology following fine-needle aspiration (FNA). While the diagnosis of PTC is usually reached through cytology, FTC diagnosis is more challenging, since the cytological distinction between benign follicular adenoma (FTA) and FTC and their variants Hürthle cell adenoma (HCA) and Hürthle cell carcinoma (HCC) is hard to reach, and a determination cannot be reached in 10 to 30% of the cases. In addition to FTA and FTC the differential diagnosis of indeterminate thyroid nodules from FNA cytology may represent hyperplasia (HN) or a follicular variant papillary thyroid carcinoma (FVPTC). FVPTC diagnosis is difficult due to its overlapping features with both benign and malignant follicular thyroid lesions. Most of the cases require a subsequent histological evaluation of capsular and/or vascular invasion. In addition to FNA being inconclusive, diagnostic discrepancies also occur in the final histology for minimally invasive FTC, PTC, and hyperplastic nodules. The co-PI's laboratory has developed and validated in close collaboration with Dr. Cerutti, a Professor at the Federal University of Sao Paulo, Brazil, a series of antibody markers that can accurately distinguish between a wider variety of benign and malignant thyroid lesions in fixed sections and FNA samples. Published results show that the set of antibodies had a sensitivity between 0.91 and 1.0 (depending on the antibody), and a specificity between 0.87 and 0.9 for distinguishing a follicular adenoma from FTC. Hürthle cell adenomas were later identified as the culprit for keeping the specificity at about 0.85. However, a marker specific for Hürthle cell adenoma was identified, and when used in conjunction with the carcinoma biomarkers, it eliminated the Hürthle Cell adenoma false positives, yielding nearly perfect combined sensitivity and specificity for detecting malignancy, when the test is performed by experienced technicians. Further investigation also revealed biomarkers of PTC, which are useful for detecting occult cancer cells that have metastasized to the lymph node.

Specific Aims

The objectives of this project were to elucidate the reasons for the increased incidence of thyroid cancer among WTCHP participants, and to explore the behavior of these cancers. This project investigated whether thyroid cancers among WTCHP participants differed from a clinical, epidemiologic and molecular viewpoint from thyroid cancers in WTC-unrelated patients.

The specific aims of the project were:

Aim 1. **To analyze if thyroid cancer over-diagnosis occurred among WTCHP because of increased surveillance.** We compared clinical characteristics of thyroid cancer tumors diagnosed within WTCHP with those characteristics of a group of thyroid cancers who are WTC-unrelated, frequency matched by gender and race. The hypotheses were that over-diagnosis due to screening will result in a large number of early stages thyroid cancers among WTCHP. Tumor clinical characteristics (tumor stage, size, nodal involvement, local and distant metastatic spread), distribution of classic thyroid cancer risk factors, and medical history (frequency of medical visits and of chest imaging, diagnosis because of symptoms vs. asymptomatic finding during medical surveillance) were compared between WTC and non-WTC cases. This helped dissect whether excess cancer incidence reflects a real increase in risk or is due to over-diagnosis from medical surveillance.

Aim 2. **To test if over-diagnosis of malignant thyroid cancer occurred among WTCHP responders**. A panel of molecular markers that distinguish benign from malignant carcinoma was tested in archived thyroid cancer tissue from WTC responders and non WTC related thyroid cancers. The expression of 4 genes (DDIT3, PVALB, ITM1, and C1orf24), which were found to be able to accurately discriminate between benign and malignant thyroid follicular, papillary and Hurtle cell carcinoma were tested as a standard to eliminate false positives for the diagnosis of malignancy. Currently there is uncertainty in scoring a thyroid cancer as malignant based on histopathology alone. We hypothesized that a false diagnosis of malignancy was more likely to occur among WTC responders than in non WTC thyroid cancers, because of increased surveillance and a more conservative approach towards this population.

This project represents the first in-depth epidemiologic and molecular analysis of thyroid cancer excess among WTC rescue and recovery workers. The results have important implications in terms of surveillance and care and important implications on the surveillance and clinical management of thyroid cancer, a frequent cancer among WTCHP members. It also represents the first step to a more extensive study involving cases from the other two WTC exposed cohorts, where thyroid cancer is also shown to have a statistically significant increase.

Methodology

The project addressed two separate but complementary aims. It focused on cases of thyroid cancer identified within the WTCHP and from the Department of Otolaryngology at Mount Sinai. Data was obtained from existing medical and epidemiological records and from additional contacts with patients; tumor samples were obtained from the pathology archives.

Aim 1- **To analyze whether thyroid cancer over-diagnosis occurred among WTCHP participants due to increased surveillance.**
A follow-up for cancer incidence is routinely performed within the WTCHP. Cancer incidence information has been published up to 2008 [Solan et al., 2013], and a new follow-up to 2010 has been recently completed. The WTCHP ran a preliminary estimate of the number of cases confirmed by the cancer registry or certified by the WTCHP up to 2012. The current number of thyroid cases is 203, of which 148 have agreed to be part of a research program (Table 3).

Table 3 - Number of thyroid cancer cases in the WTCHP cohort	Certification or registry confirmed	Certification only
Total number of thyroid cases	203	156
Consented to aggregate data	190	147
Consented to be contacted	**148**	109

Newly diagnosed, incident cases of thyroid cancer were identified through this mechanism, and asked for permission to access their medical and epidemiologic records, their tissue sample, and to answer a brief additional epidemiologic questionnaire.
Information on tumor clinical characteristics, personal and medical history, prevalence of thyroid cancer risk factors, and medical history specific to thyroid cancer diagnosis were compared between cases diagnosed among WTC responders, and a group of gender-, and race-frequency matched thyroid cancer cases treated at Mount Sinai (control group) during the same period. The Department of Otolaryngology has an active research data base of all treated thyroid cancer cases (Dr Genden, Chairman of the Department of Otolaryngology, is a co-investigator in this grant) from which we obtained the non WTC control group.

Details on information collected: tumor clinical characteristics include histology, stage (TNM), tumor size, node involvement, local and distant metastatic spread. Personal and medical history include demographics (place of birth, year of immigration for those born outside of the US), personal history of any benign thyroid condition. Risk factors include smoking status, family history of thyroid cancer, personal history of any cancer treated with radiotherapy, history of exposure to radiation and of childhood exposure to nuclear sources; medical history specific to thyroid cancer diagnosis include frequency of medical visits, diagnosis because of symptoms vs. asymptomatic finding during medical surveillance.
An excess of cases diagnosed at early ages and at early stages, as well as an excess of asymptomatic findings in the WTCHP suggests excess diagnoses due to surveillance. The information on potential risk factors serves the purpose of assessing if WTC cases experienced exposure to known thyroid cancer risk factors in the same proportion or rather at a higher proportion than non-WTC cases, and if that excess exposure could explain the observed high incidence of thyroid cancer cases in the WTC cohort.

Some of the needed information were collected through the available data bases: the WTCHP for the WTC cases, and the Department of Otolaryngology for the non WTC cases. In addition, medical records were actively searched for additional information on tumor characteristics. Pathology reports were obtained for the majority of cancer cases by the WTCHP in order to confirm the diagnosis; other types of medical records (e.g., discharge letters) were obtained from approximately half of the patients. Full medical records including pathology reports were available from control patients diagnosed and treated at Mount Sinai.
In addition, both WTC patients and controls were mailed a standard questionnaire aimed at collecting the missing information on risk factors and personal/medical history.
Following the successful design that we implemented for the prostate cancer study (5U01OH010396, PI: Dr. Taioli), patients who agreed to be contacted (n= 148), were mailed a letter informing them about the study and asking them to contact our projects assistant if interested in participating. Once they call showing interest, we followed up with them and offered the option to consent and complete the questionnaire on internet.
A comparison of WTCHP cases with the thyroid cancer cases included in the NY State Cancer Registry was also carried out for those epidemiological and clinical characteristics that are recorded in the registry.
Statistical analysis: This analysis tested the hypothesis that those patients with WTC-related thyroid

cancers have increased “high risk” disease compared to controls. In the first set of analyses, each clinical characteristic defining the patient as having a high risk disease (stage, tumor size, nodal involvement, local and distant metastatic spread) among WTCHP patients was compared with that of controls using a t-test or Wilcoxon Rank Sum test for continuous variables, and chi-square or Fisher’s Exact test for categorical variables. Multivariate logistic regression was then used to calculate odds ratios (OR) and 95% CI for high risk disease between cases and controls after adjustment for type of therapy, socio-economic status, and any matching variables that are differentially distributed between cases and controls. The distribution of thyroid cancer risk factors, such as exposure to ionizing radiation was compared between WTC cases and controls, and included in the multivariable models as adjustment factors.

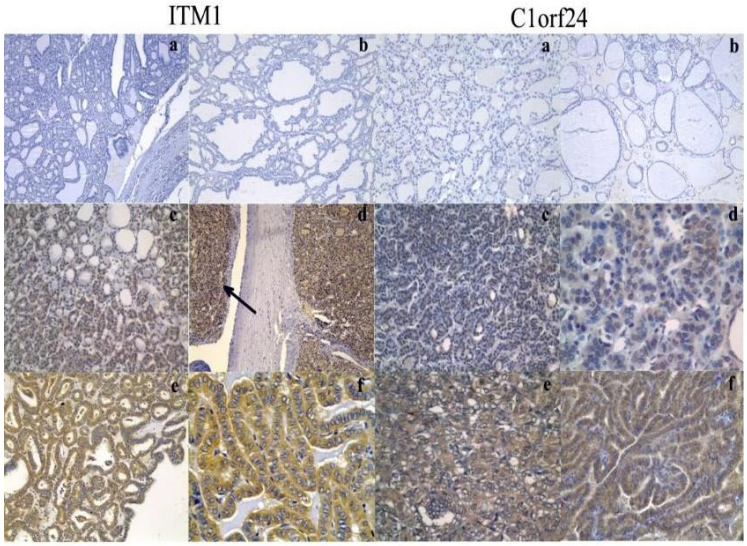
In the second set of analyses, medical history (frequency of medical visits, diagnosis because of symptoms vs. asymptomatic finding during medical surveillance) was compared between WTC-related cancers and controls. This analysis tested the hypotheses that (i) a higher proportion of WTC-related cases had their cancer diagnosed as a result of medical surveillance than controls and (ii) they had a higher number of chest imaging tests during the five-year period preceding their diagnosis than controls.

Aim 2. **To test if over-diagnosis of malignant thyroid cancer occurred among WTCHP responders**. A panel of molecular markers that distinguish benign from malignant carcinoma were tested in archived thyroid cancer tissue from WTC responders and non WTC related thyroid cancers.

The expression of 4 proteins (DDIT3, PVALB, ITM1, and C1orf24), which were found to be able to accurately discriminate between benign and malignant thyroid follicular, were tested in papillary (including FVPTC) and follicular thyroid carcinoma (including its variant HCC) as a standard to eliminate false positives for the diagnosis of malignancy. Currently there is uncertainty in scoring a thyroid cancer as malignant based on histopathology alone. We hypothesized here that a false diagnosis of malignancy is more likely to occur among WTC responders than in non WTC thyroid cancers, because of increased surveillance and a more conservative approach towards this population.

Laboratory methods: For follicular and Hürthle cell histology of the thyroid tumors we employed a set of three proven antibodies to accurately discriminate between malignant and benign tumors with sensitivity and specificity close to 100%.

Figure 1 - Thyroid Carcinoma Antibody Markers for ITM1 and C1orf24 stain strongly with high sensitivity and specificity for malignant thyroid cells, and are a clinically useful tool for establishing the correct diagnosis. IHC of ITM1 and C1orf24 in paraffin-embedded sections of Follicular Thyroid Adenoma- FTA (a), Hyperplasia-HN (b), FTC (c,d), Follicular Variant of Papillary Thyroid Carcinoma- FVPTC (e) and PTC (f). Malignant tumors, FTCs, FVPTC and PTC, exhibited strong brown immunostaining for ITM13 and



C1orf24. In contrast, the benign tumors FTA and HN showed no staining. The arrow in d shows the vascular invasion in FTC and the follicular cells that are positive for ITM1. FTC exhibited both nuclear and cytoplasm staining with anti-C1orf24 (c,d). Anti-ITM1 was used at a dilution of 1:100 and anti-C1orf21 at a dilution of 1:200. Original magnification is X200, except for C1orf24 d and e where original magnification is X400. Figure is adapted from Cerutti, et al. Clin Cancer Res 12(11), 3311-17, 2006.

The goal of these experiments is to confirm the pathologist's histological diagnosis, and using the markers as a standard, determine the false positive rate for malignancy. Follicular thyroid tumors are notorious for misdiagnosis because the histopathological documentation of capsular invasion requiring complete resection of the tumor is easy to miss, sometimes resulting in a defensive over-diagnosis to avoid missing any malignancies. In our previous studies, using this panel of markers has allowed us to refine the correlation with patient outcomes.

Using fixed tissue sections of tumors with the pathological diagnosis of follicular or Hürthle thyroid cancer from WTCHP responders, we first used two markers that stain for malignant tumors and discriminate between Follicular Thyroid Adenoma (FTA) and FTC with high sensitivity (1.00) and specificity (0.85) (Figure 1). Custom antibodies for ITM1 and C1orf24, as described in previous studies, were used as immunohistochemical biomarkers. We have previously shown that immunohistochemistry (IHC) was more sensitive than quantitative PCR in detecting thyroid carcinomas, and that the combination of markers was more effective than a single marker.

Although this antibody-based test with just four markers had high sensitivity (1.0), the specificity was lower (0.85) (with two of four markers subsequently shown as being redundant). The false-positive cases were found within a small subset of the benign Hürthle cell adenomas (HCA) tumors, which were positive for carcinoma markers. However, using the same approach, Dr. Cerutti working on sabbatical at Johns Hopkins University was able to identify and confirm PVALB as a new HCA marker, to eliminate these false positives. This marker was negative in a wide range of thyroid carcinomas, but positive for HCAs.] Therefore, PVALB antibodies were additionally used for immunohistochemistry analysis on the WTCHP responder tumor tissue sections to identify any false positives from HCA, a benign tumor. The classification schema is shown in Figure 2. Our studies were consistent with our previous findings and also demonstrated that C1orf24 is the best predictor among the four carcinoma markers, followed by ITM1, and DDIT3 being redundant for the detection of malignancy. Although we could perform the test for detecting malignancy with just C1orf24 (and PVALB for HCA), to be more thorough we tested additionally with ITM1 and DDIT3, for a total of four markers (Figure 2). Therefore in this study there were three well-vetted antibodies to detect

follicular thyroid malignancy at 100% sensitivity. Although other thyroid cancer pathological diagnoses, such as PTC, are much more accurate than the follicular histology, we tested the panel of markers on these tumors as well, given that follicular variant of PTC might be a source of diagnostic error.

We also compared the results to historical results from our previous studies, to ensure that the assay is functioning properly. Controls for all of the IHC tests include positive and negative controls for each antibody. For example, for PVALB, we had sections from a HCA that test positive, and a Hürthle Cell Carcinoma that tests negative, to ensure the antibody is successfully detecting benign tumors

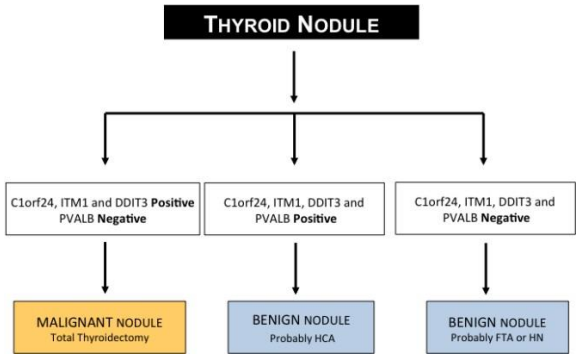


Figure 2- Diagnostic schema using a panel of diagnostic antibodies to distinguish benign from malignant thyroid tumors. When antibodies for proteins C1orf24, ITM1 detect their respective targets, the tumor is most likely malignant, except in the rare case when it is a Hürthle Cell Adenoma (HCA). These are identified if PVALB stains positive. DDIT3 serves the same purpose as C1orf24, ITM1, making the detection of malignancy, the most important aspect, triply redundant. FTA, follicular thyroid adenoma; HN, hyperplastic nodule.

For those cases where discordance is observed between the pathology diagnosis of malignancy and the immunohistochemistry test disproving the malignancy, further in depth laboratory tests were performed employing target next generation sequencing to find mutations and fusions based on a thyroid diagnostic test developed at the University of Pittsburgh [Nikiforova, Wald et al. 2013]. In this test nanogram amounts of DNA extracted from the paraffin embedded sample were sequenced for mutational hotspots in the *BRAF, RAS, PIK3CA*, *TP53*, *TSHR*, *PTEN*, *GNAS*, *CTNNB1*, AKT1, TERT, EIF1AX and *RET* genes.

Statistical Analysis: The immunohistochemistry markers were scored according to the intensity of staining in three categories: weak (+), moderate (++), and strong (+++); a negative staining was recorded as well. A staining of moderate to strong intensity for C1orf24, ITM1, with no staining for PVALB, was considered positive for malignancy. Cancer samples were reclassified as positive or negative for malignancy according to the HCA test; subsequently, we compared the false positive rate of malignant thyroid cancer among WTC responders with that of non-WTC thyroid cancer patients using chi-square and Fisher exact tests.

Results

Specific aim 1:

There were 73 thyroid cancer cases from the WTCHP cohort and these were compared to 949 thyroid cancer cases from the Mount Sinai Cancer Registry. The majority of thyroid cancer cases were white, both in the WTCHP group (71.9%) and in the Mount Sinai Cancer Registry (70.2%) ($p = 0.8$). There was, however, a statistically significant difference in gender ($p < 0.0001$), with WTCHP cases more likely to be male (78.1%). There was no significant difference between the two groups in terms of tumor size ($p = 0.4$), and the mean tumor size was small in both the WTCHP and the Mount Sinai group, 1.4 cm and 1.8 cm, respectively. Age at diagnosis was also similar between the two groups ($p = 0.2$); the mean age for those diagnosed after WTC exposure was 48.9 years while the Mount Sinai Registry mean diagnosis age was 51 years old. There was a statistically significant difference in terms of histology ($p = 0.04$), with those in the WTCHP cohort more likely to be diagnosed with a subtype of papillary carcinoma. There was also a statistically significant difference between the WTCHP and Mount Sinai group in terms of smoking ($p = 0.0385$), whereby those in the WTCHP group were more likely to be current smokers, and in terms

of marital status ($p < 0.0001$), with those in the WTCHP cohort being more likely to be married (Table 4). Out of the 69 eligible WTC thyroid cancer cases, 35 (51%) consented to complete the questionnaire. Those who consented and completed the questionnaire did not differ significantly in terms of race, gender, age at diagnosis or histology than those who did not participate in the study (data not shown). A total of 23% of cases reported some sort of radiation exposure. While only 9% reported a family history of thyroid health issues (either a benign goiter or thyroid cancer), 67% reported a family history of other cancer types. Additionally, 21% reported a previous history of cancer before the diagnosis of thyroid cancer. The majority of the study cohort had a BMI between 25 and 30 Kg/m2 (44%) or >30 kg/m2 (44%). Most participants (62%) reported that their thyroid cancer was diagnosed as a consequence of routine or incidental medical surveillance, and not because they went to a doctor with symptoms consistent with thyroid cancer (Table 5).

Table 4. Description of World Trade Center Health Program (WTCHP) and Mount Sinai Registry thyroid cancer cases.

Demographic and Clinical Characteristics *	WTCHP (n = 73)		Sinai Cancer Registry (n = 949)		p Value
	n	%	n	%	
Race/Ethnicity					0.8177
White	41	71.9	634	70.2	
Black	3	5.3	68	7.5	
Other	13	22.8	201	22.3	
Gender					<0.0001
Female	16	21.9	695	73.3	
Male	57	78.1	253	26.7	
Tumor Size (cm)	Mean (1.4)	SD (1.2)	Mean (1.8)	SD (1.9)	0.4053
Age at Diagnosis	Mean (48.9)	SD (8.0)	Mean (51.0)	SD (16.2)	0.2252
Histology ^					0.0363
Papillary Carcinoma	66	90.4	792	83.5	
Papillary Adenocarcinoma NOS	(63.6%)		(58.7%)		
Papillary Carcinoma Follicular Variant	(28.8%)		(22.0%)		
Papillary Microcarcinoma	(3.0%)		(17.7%)		
Papillary Carcinoma Columnar Cell	(4.5%)		(1.6%)		
Other Adenocarcinoma	5	6.9	41	4.3	
Oxyphilic Adenocarcinoma	(60.0%)		(46.3%)		
Follicular Adenocarcinoma	(40.0%)		(53.7%)		
Other	2	2.7	116	12.2	
Smoking Status					0.0385
Current Smoker	3	5.1	14	1.5	
Former or Never Smoker	56	94.9	925	98.5	
Marital Status					<0.0001
Married or Partnered	42	70.0	519	59.7	
Separated or Divorced	12	20.0	56	6.4	
Single	3	5.0	241	27.7	
Widowed	3	5.0	53	6.1	

* Race n_{WTC} = 57, $n_{registry}$ = 903; gender n_{WTC} = 73, $n_{registry}$ = 948; tumor size n_{WTC} = 27, $n_{registry}$ = 753; age at diagnosis n_{WTC} = 73, $n_{registry}$ = 949; histology n_{WTC} = 73, $n_{registry}$ = 94, marital status n_{WTC} = 60, $n_{registry}$ = 869. ^ Histology is based on International Classification of Diseases for Oncology (ICD-O-3) coding: Papillary adenocarcinoma NOS = 8260, oxyphilic adenocarcinoma = 8290, follicular adenocarcinoma NOS = 8330, papillary carcinoma follicular variant = 8340, papillary microcarcinoma = 8341, papillary carcinoma columnar cell = 8344.

Table 5. WTC thyroid cases questionnaire responses (n = 35).

Exposures and Medical History *	n	%
Radiation Exposure		
Yes	8	22.9
No	27	77.1
Family History of Thyroid Issues		
Yes	3	8.8
No	31	91.2
Family History Other Cancer		
Yes	22	66.7
No	11	33.3
Personal History of Another Cancer		
Before Thyroid Cancer	7	20.6
After Thyroid Cancer or Unknown dx Date	8	23.5
No Other Cancer	19	55.9
BMI (kg/m^2)		
<25	4	11.8
25–30	15	44.1
>30	15	44.1
Diagnosis Method		
Because of Symptoms	21	61.8
Due to Routine Screening or Unrelated Medical Event	13	38.2

* Missing data for family history of other cancer (1), family history of other cancer (2), personal history of other cancer (1), smoking history (1), BMI (1), diagnosis method (1).

Specific aim 2:

There were 73 participants in the WTC cohort of responders who were eligible to be included in this study, four of whom had to be excluded as they did not speak English or because they had no viable contact information. Of the remaining 69 WTC thyroid cancer patients, 37 patients (54%) consented to participate. We were able to obtain FFPE thyroid tumor tissue samples for 30 WTC participants. The comparison of the 30 WTC thyroid cancer patients who consented and the 43 remaining WTC thyroid cancer patients showed that the groups were not significantly different for age at diagnosis, gender, and histology (Table 6).

Table 6. Characteristics of the study sample.

Clinical–Pathological Features	**WTC thyroid cancer cases**			**Non-WTC controls**	
	eligible (*n* = 43)	**included (n = 30)**	**P value [a]**	**included (n = 30)**	**P value [b]**
Age at Diagnosis (years)	48.5 (SD 7.7)	49.3 (SD 8.6)	0.65	47.8 (SD 11.3)	0.5652
Gender			0.16		1.00
Male	36 (83.7%)	21 (70%)		21 (70%)	

Female	7 (16.3%)	9 (30%)		9 (30%)	
Histology			0.74		1.00
Papillary thyroid carcinoma	27 (62.8%)	21 (70%)		21 (70%)	
Papillary thyroid carcinoma, follicular variant	12 (27.9%)	6 (20%)		6 (20%)	
Other	4 (9.3%)	3 (10%)		3 (10%)	
Tumor Size[c] (cm)	-	1.38 (SD 1.16)	-	1.46 (SD 0.93)	0.78
Microcarcinoma					
Yes[c]	-	14 (51.85%)	-	12 (40.0%)	0.37

[a] Eligible versus included WTC thyroid cancer cases; [b] Included WTC versus non-WTC thyroid cancer cases; [c] Tumor size unknown for 3 WTC cases; WTC: World Trade Center.

After matching, the WTC- and the non-WTC thyroid patient groups were well balanced in terms of age at diagnosis (p = 0.57), gender (p = 1.00), and histology (p = 1.00) (Table 6). Evaluation of clinical and pathological characteristics showed that there was no statistically significant difference in terms of tumor size (p = 0.77). Microcarcinomas, defined as thyroid cancer ≤1cm, were found in 52% of the WTC thyroid cancer patients compared with 40% in the non-WTC thyroid cancer patients (Table 6). Antibody assessment correctly classified thyroid nodules in either group (Figure 3).

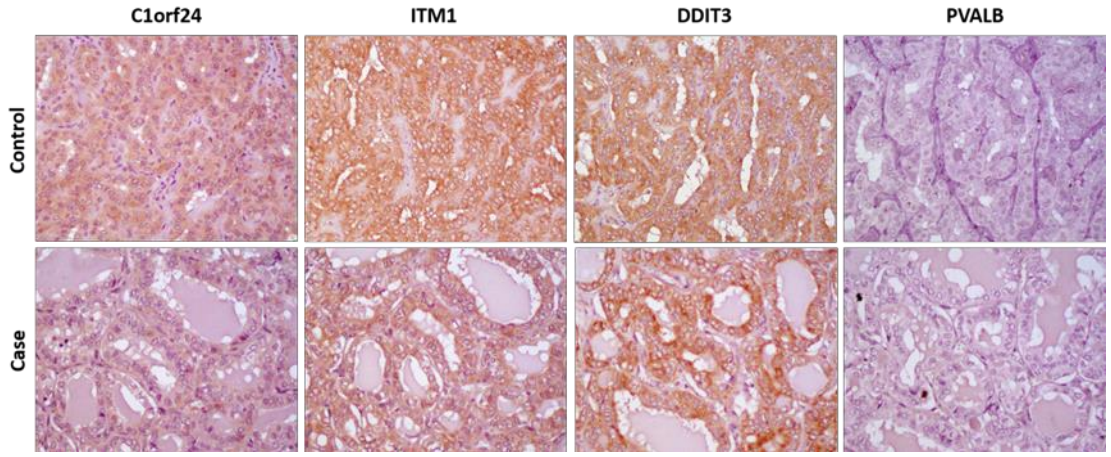


Figure 3. Representative results of molecular markers in WTC and non-WTC thyroid carcinomas (original magnification of x40).

Except for three thyroid samples, all thyroid tumor tissue samples from thyroid tissue from the two groups and all histology types tested positive for malignancy with antibodies C1orf24, ITM1, and DDIT3 and negative PVALB. For the other three samples (two WTC cases and one

control), it was not possible to detect actual tumor tissue in the slides used for immunohistochemistry, and therefore, these samples could not be confirmed as malignant in the antibody-based test; all three samples were taken from tumors originally less than 0.3 cm in size. Most of the tumors had a strong brown staining for three markers (DDIT3, ITM1, and C1orf24) and no staining for the benign Hurthle adenoma marker (PVALB) (Figure 2).

Discussion

Specific aim 1:

Whether or not surveillance bias is occurring in the WTCHP cohort, and the extent to which this bias may be contributing to the increased incidence of thyroid cancer among first responders, remains unclear. The similar clinical characteristics observed between the WTCHP responders and those in the Mount Sinai Registry suggest that the excess risk of thyroid cancer in first responders cannot be adequately explained by surveillance bias alone. Under the surveillance bias hypothesis, we would expect increased detection of small thyroid nodules, yet there was no statistical difference between the average tumor size of the WTCHP and Mount Sinai Registry groups. Moreover, the average age at diagnosis was similar between the two groups, while if surveillance bias was introduced then smaller cancers should have been detected at an earlier age in the WTC cohort. It is important to consider how surveillance bias may be occurring across the US as a whole; previous research had found that much of the national increase in thyroid cancer incidence can be attributed to an increase in small (<1 cm) tumors, unlikely to be found in the absence of routine or incidental surveillance.

Moreover, the majority of WTC participants reported that their cancers were diagnosed due to routine or incidental screening, which may be higher than the expected rate of asymptomatic thyroid cancer detection.

The WTCHP and Mount Sinai thyroid cancer groups statistically differed in terms of gender, histology, smoking history and marital status; they were not statistically different in terms of race. Comparison of gender between the two groups, however, is difficult to interpret, since the WTCHP is composed predominantly of males. WTCHP thyroid cancer cases were more likely to be papillary histology, which tend to have a favorable prognosis. Moreover, those in the WTCHP cohort were more likely to be current smokers when compared to the Mount Sinai Registry group, though the number of reported current smokers was small for both groups. It remains controversial what affect smoking has on thyroid cancer risk; a decrease in risk of thyroid cancer in men who are current smokers has actually been observed, although there is no known biological justification for this.

WTCHP respondents with thyroid cancer were also more likely to be married or have a partner; data indicate reduced mortality from cancer associated with being married as opposed to being single, possibly because of increased social support.

While WTCHP thyroid cancer cases do not appear to be clinically distinct, their reported risk factors and carcinogenic exposure history may be uncommon. Only about 23% reported having had some sort of previous diagnostic radiation exposure before their thyroid cancer diagnosis, while other studies have found that this number could be as high as 85%, even suggesting this type of radiation exposure contributes to the carcinogenic process.

Increased BMI is also associated with increased risk of thyroid cancer and 44.1% of WTCHP responders reported a BMI 25–29 km/m2, with an additional 44.1% reporting a BMI >30 km/m2. Neta et al. reported 15.9% and 12% of the thyroid cancer cases having a BMI of 25–29, and _30 km/m2, respectively, which is lower than what was observed in the WTCHP cohort. However, these percentages seem to be in keeping with what has been reported for the overall WTCHP

general responder cohort, suggesting that the thyroid cancer cases represent a random subset of the total group in terms of BMI.
Moreover, few WTCHP responders (8.8%) reported in their questionnaire that they had a family history of thyroid cancer or benign thyroid issues. Having a first-degree relative with thyroid cancer is known to increase thyroid cancer risk. Other studies have found that as high as 15.6% of thyroid cancer cases report a family history of thyroid cancer. A family history of another malignant disease has also been shown to be associated with thyroid cancer, and having a family history of cancer was reported by 66.7% of WTCHP respondents. This is higher than reported by past research, which found that 49% of thyroid cancer cases reported a family history of cancer in first-degree relative. It is possible that some WTC respondents may have reported past cancers of relatives more distant than first-degree relatives, thus inflating the statistic. Having a previous cancer diagnosis has also been shown to be associated with thyroid cancer, and 20.6% of WTCHP respondents reported having had another cancer before being diagnosed with thyroid cancer. This is higher than what was reported in the SEER database, where only 10.9% of thyroid cancer cases had another cancer predating thyroid cancer diagnosis. It is possible that this is related to the fact that WTC responders are at an increased risk for several types of cancer, including prostate cancer; an alternative explanation could be an increased familial risk among WTCHP responders. The WTCHP responders were also likely (23.5%) to develop a second primary cancer after thyroid cancer, which is in keeping with the observed increase in risk of secondary cancers associated with a primary thyroid cancer. This number is higher, however, than what would be expected based on SEER registry data, whereby just 8% of thyroid cancer cases developed a second type of tumor. Again, it remains unclear if this increased risk of multiple primary cancers is because of WTC dust and debris exposure having a carcinogenic effect on 9/11 first responders or because of other genetic or environmental factors.
This study had some limitations, which includes a small sample size that may have been affected by recall bias, since participants were asked about past exposure and family history. Although selection bias could have been possible, an attempt was made to verify that those who participated were not statistically different from those who chose not to.
Among the strengths, this study represents an important contribution to the literature by helping to fill the gap in understanding why 9/11 first responders experience an increased risk of thyroid cancer. The descriptive epidemiology presented here will inform future, more in-depth studies that may explain this phenomenon. Future research on germline and somatic tumor alterations of these cancers may help to shed light on the possibility of a WTC-related carcinogenic mechanism.

Specific aim 2:

The findings of the present study suggest that over diagnosis by virtue of misdiagnosis of a benign tumor as malignant does not explain the increased incidence of thyroid cancer observed in WTC responders. If over diagnosis were occurring, we would expect an excess of false-positive malignancies among WTC thyroid cancer cases; benign tumors would be detected because of enhanced screening efforts and diagnosed as malignant because of physician bias associated with knowing that the patient has a history of WTC exposure. However, there was not an excess of false-positive thyroid cancer diagnoses found among the WTC thyroid cancer cases. In fact, none of the WTC thyroid cancer tumors assessed were false-positives; instead, all samples tested using the antibody-based cancer panel were determined to be true malignant disease. Although it may still be that physicians treating WTC responders may have biases that make them more likely to defensively diagnose nodules as thyroid cancer to avoid missing malignancies, our results suggest that screening of WTC responders, at least in the case of thyroid cancer, may not be unwarranted.

It is important to note that surveillance bias may still be occurring in this cohort. Surveillance bias occurs when increased screening efforts result in nodules being detected that would otherwise have gone unnoticed given routine surveillance, thus inflating the actual incidence of disease in a heavily screened population. Smaller tumor size and younger age at diagnosis in the WTC cohort would generally be suggestive of surveillance bias, but the design of the present study does not allow any such conclusions to be drawn. For this study, WTC and non-WTC cases were matched by age, gender, and histology; thus, it is expected that age and tumor size are similar between the two groups. However, a descriptive study of the WTC thyroid cancer cases showed that these cases had similar clinical characteristics as thyroid cancer cases in the Mount Sinai registry in terms of age at diagnosis and tumor size, suggesting that surveillance bias alone cannot explain the excess risk of thyroid cancer in WTC responders,

Being that the increased risk of thyroid cancer in WTC responders does not appear to be an artifact due to physician bias, the results of this study leave open the possibility of an as-yet unknown carcinogenic mechanism through which WTC exposure is acting on thyroid cancer carcinogenesis. The biological basis of the tumors of WTC responders, including thyroid cancer tumors, warrants further research.

This is the first study to investigate the possible reasons for the increased incidence of thyroid cancer in the WTC population and the first to show that over-diagnosis due to physician bias does not appear to adequately explain the observed excess risk. The study is also novel in that it is the first to utilize biomarkers of malignancy in a WTC cohort. A further strength of this study is the high rate of compliance, with 54% of eligible WTC thyroid cancer patients agreeing to have their tumor sample molecularly analyzed.

This study is limited in that not all tumor samples could be retrieved from the institutions where the thyroid cancer surgery was performed and that, for a few samples, there was no tissue sample in the slides provided. However, this was a small portion of the samples (5%). In addition, a comparison of the characteristics of those patients for which we obtained a sample to the characteristics of the eligible patients does not show any difference in personal or tumor characteristics, thus reducing the possibility of selection bias.

Further analysis is needed to investigate a causal link between thyroid cancer in WTC-responders and high levels of exposure to potentially carcinogenic agents at Ground Zero, which may result in cancers with a shorter latency period, similar to that observed in individuals exposed to iodine-131 after the Chernobyl accident. It is well known that patients exposed to Chernobyl fallout demonstrated a linear dose–response association. Therefore, to define whether there is a correlation between the levels of exposure to the debris cloud and thyroid cancer, diagnosis is needed, as well as a longer follow-up.

Additionally, the investigation of somatic events that drive thyroid cancer pathogenesis in this cohort, concomitant to longer follow-up and correlation with clinical-pathological features, will increase our knowledge of whether the molecular events in WTC responders differ from those not exposed to the dust cloud, as well as better define tumor aggressiveness.

Conclusion

Specific aim 1:
We did not observe signs of over diagnosis due to frequent screening; the result suggest that cancer surveillance of WTC first responders should continue, and specifically thyroid health should be part of regular screening procedures. Ultrasound techniques instead of radiation-based diagnostic procedures might be a more appropriate first step approach in this population.

Specific aim 2:
From our molecular study we did not observe any benign cases diagnosed as malignant thyroid cases. We concluded that rather than over diagnosis of false-positives due to physician bias, it might instead be the case that the yearly screening visits by the WTCHP are identifying true cases of thyroid cancer earlier, increasing the possibility of a favorable prognosis, which warrants regular screening of this cohort.

Publications

1. Tuminello S, van Gerwen MAG, Genden E, Crane M, Lieberman-Cribbin W, Taioli E. Increased Incidence of Thyroid Cancer among World Trade Center First Responders: A Descriptive Epidemiological Assessment. Int J Environ Res Public Health. 2019 Apr 9;16(7):1258.

2. van Gerwen MAG, Tuminello S, Riggins GJ, Mendes TB, Donovan M, Benn EKT, Genden E, Cerutti JM, Taioli E. Molecular Study of Thyroid Cancer in World Trade Center Responders .Int J Environ Res Public Health. 2019 May 7;16(9):160

PHS Inclusion Enrollment Report

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 10/31/2018

*Study Title (must be unique): **Thyroid cancer risk among WTC responders**

*** Delayed Onset Study?** ☐ **Yes** ☒ **No**

If study is not delayed onset, the following selections are required:

Enrollment Type ☐ Planned ☒ Cumulative (Actual)

Using an Existing Dataset or Resource ☒ Yes ☐ No

Enrollment Location ☒ Domestic ☐ Foreign

Clinical Trial ☐ Yes ☒ No **NIH-Defined Phase III Clinical Trial** ☐ Yes ☒ No

Comments:

Racial Categories	**Ethnic Categories**									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			**Total**
	Female	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	2	0	0	0	0	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	8	6	0	16	2	0	0	0	0	32
White	64	30	0	14	4	0	0	0	0	112
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	2	2
Total	72	38	0	30	6	0	0	0	2	148

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Tuminello S, van Gerwen MAG, Genden E, Crane M, Lieberman-Cribbin W, Taioli E. Increased Incidence of Thyroid Cancer among World Trade Center First Responders: A Descriptive Epidemiological Assessment. International journal of environmental research and public health. 2019 April 9;16(7). PubMed PMID: 30970543; PubMed Central PMCID: PMC6479621; DOI: 10.3390/ijerph16071258.
N/A: Not NIH Funded	van Gerwen MAG, Tuminello S, Riggins GJ, Mendes TB, Donovan M, Benn EKT, Genden E, Cerutti JM, Taioli E. Molecular Study of Thyroid Cancer in World Trade Center Responders. International journal of environmental research and public health. 2019 May 7;16(9). PubMed PMID: 31067756; PubMed Central PMCID: PMC6539993; DOI: 10.3390/ijerph16091600.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
TAIOLI	Y	TAIOLI, EMANUELA	MS,PHD,MD	PD/PI	2.1	0.0	0.0			NA
GRIGGIN1	Y	RIGGINS, GREGORY Joseph	BS,MS,PHD,MD	PD/PI	0.7	0.0	0.0			NA
	N	Alpert, Naomi		Biostatistician	6.0	0.0	0.0			NA
	N	Gillezeau, Cristina		Clinical Researcher	5.1	0.0	0.0			NA
	N	Lieberman-Cribbin, Wil		Research Assistant	5.7	0.0	0.0			NA
	N	Benn, Emma		Co-Investigator	1.0	0.0	0.0			NA
	N	Liu, Bian		Co-Investigator	1.8	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Our project presents important implications on the surveillance and clinical management of thyroid cancer, a frequent cancer among WTCHP members, by showing that increased surveillance is warranted. It also represents the first step to a more extensive study involving cases from the other two WTC exposed cohorts, where thyroid cancer is also shown to have a statistically significant increase.

Disentangling the effect of WTC-related exposures on clinical cancer characteristics and incidence is a particularly important aspect in thyroid cancer. Excess diagnoses of a thyroid malignancy may lead to excess head and neck surgery via thyroidectomy, an approach that carries a sizable risk of complications. Patients may also require supplemental life-long replacement therapy in tandem.

Testing thyroid samples with the proposed set of antibodies biomarkers may become the recommended clinical practice to be added to the diagnostic tools for thyroid cancer, especially within the WTC first responder population, and could be recommended to improve the diagnostic accuracy of suspicious thyroid nodules from both tissue sections and FNA samples.

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
Enrollment Table 1026.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

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I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

Our project presents important implications on the surveillance and clinical management of thyroid cancer, a frequent cancer among WTCHP members, by showing that increased surveillance is warranted. It also represents the first step to a more extensive study involving cases from the other two WTC exposed cohorts, where thyroid cancer is also shown to have a statistically significant increase.

Disentangling the effect of WTC-related exposures on clinical cancer characteristics and incidence is a particularly important aspect in thyroid cancer. Excess diagnoses of a thyroid malignancy may lead to excess head and neck surgery via thyroidectomy, an approach that carries a sizable risk of complications. Patients may also require supplemental life-long replacement therapy in tandem.

Testing thyroid samples with the proposed set of antibodies biomarkers may become the recommended clinical practice to be added to the diagnostic tools for thyroid cancer, especially within the WTC first responder population, and could be recommended to improve the diagnostic accuracy of suspicious thyroid nodules from both tissue sections and FNA samples.

These results will also bear other important implications. They will address anxiety in the interpretation of the results produced so far, and will guide future surveillance of WTCHP members with respect to thyroid cancer. The implications of the results will go beyond the WTC populations, as they will provide unique and novel information on thyroid over-diagnosis due to surveillance in the US general population.