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TERT and *BRAF V600E* mutations in thyroid cancer of World Trade Center Responders

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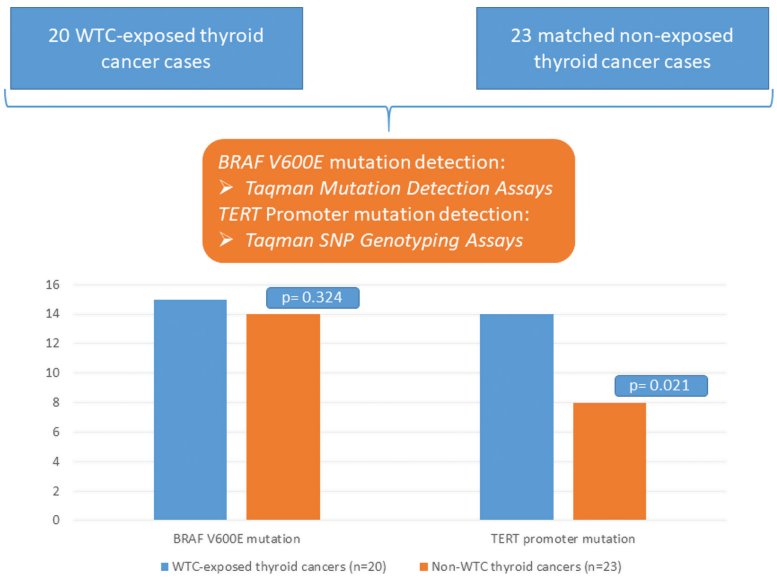
Abstract

The 2-fold excess thyroid cancer risk reported in multiple World Trade Center (WTC) disaster exposed cohorts cannot entirely be explained by surveillance and physician bias thus highlighting the need to investigate the potential consequences of the dust exposure, containing carcinogenic and endocrine disruptive elements, on the thyroid. This study investigated the presence of *TERT* promoter and *BRAF V600E* mutations in 20 WTC-exposed versus 23 matched non-exposed thyroid cancers as potential mechanism explaining the excess risk. Although no significant difference in *BRAF V600E* mutation was found, *TERT* promoter mutations were significantly more prevalent in WTC thyroid cancer versus non-exposed thyroid cancers ($P = 0.021$). The odds of a *TERT* promoter mutation was significantly higher in the WTC versus the non-WTC thyroid cancers after adjustment [OR_{adj}: 7.11 (95% CI: 1.21–41.83)]. These results may indicate that exposure to the mixture of pollutants present in the WTC dust resulted in an excess thyroid cancer risk and potentially more aggressive thyroid cancer, warranting investigating WTC responders on thyroid-associated symptoms during their health checkups. Future studies should include long-term follow-up to provide important insights in whether thyroid-specific survival is negatively affected by WTC dust exposure and whether this is because of the presence of one or more driver mutations.

Graphical Abstract



Abbreviations: CI, confidence interval; OR, odds ratio; TERT, telomerase reverse transcriptase; WTC, World Trade Center.

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Introduction

An excess thyroid cancer risk with around 2-fold increase in thyroid cancer incidence rates has been reported in multiple cohorts exposed to the World Trade Center (WTC) disaster and associated dust cloud (1–4). Although studies including a WTC-exposed fire fighter cohort and a combined rescue/recovery worker cohort concluded that medical surveillance/no-cost screening is associated with increased identification of thyroid cancer, there are also indications that screening, or surveillance does not entirely explain the observed excess risk of thyroid cancer in WTC-exposed populations (5,6). The epidemiological assessment of thyroid cancer in WTC first responders showed similar age at diagnosis and tumor size compared with Mount Sinai Registry thyroid cancer cases suggesting that early detection of small thyroid nodules due to medical surveillance of the WTC population does not solely explain the excess risk (7). Furthermore, a molecular study using a highly accurate cancer-detection four-biomarker panel to distinguish benign from malignant tumors did not identify false-positive cancers in the WTC-exposed group thus rejecting the hypothesis of overdiagnosis due to physician-associated bias (8). These findings highlight the need to further investigate the potential consequences of WTC dust exposure on the thyroid gland (9).

WTC dust analysis showed the presence of different carcinogenic and endocrine disruptive elements, including heavy metals, asbestos, flame retardants, dioxines, organic compounds (e.g. polycyclic aromatic hydrocarbons and phthalate esters) and various construction materials (e.g. powdered concrete, calcium bicarbonate, silicates) (10,11). Although exposure to certain endocrine disruptive elements may be associated with an increased risk of thyroid cancer (12), the etiology behind the WTC excess thyroid cancer risk remains unclear. Investigation of somatic events that potentially drive thyroid cancer pathogenesis will increase knowledge of potential WTC dust exposure-associated mutagenesis.

From the literature, it is known that certain genetic mutations play a role in thyroid cancer prognosis. Song *et al.* demonstrated that *TERT* promoter mutations are more frequently present in high-risk and more advanced stage groups and associated with increased recurrence risk [hazard ratio: 2.98 (95% confidence interval, CI: 1.20–7.39)] and disease-specific mortality [hazard ratio: 21.14 (95% CI: 3.60–124.23)] (13). A recent meta-analysis showed that *TERT* but not *BRAF V600E* mutations are associated with increased risk of distant metastasis, odds ratio (OR): 6.56 (95% CI: 2.24–19.23) and OR: 0.67 (95% CI: 0.29–1.58), respectively. Furthermore, co-existence of *TERT* and *BRAF V600E* mutations was associated with a 7.9-fold increased risk of distant metastases (14).

To assess whether differences in mutational patterns serve as a potential mechanism explaining the excess thyroid cancer risk among WTC responders, this study investigated the presence of *TERT* promoter and *BRAF V600E* mutations in thyroid cancers among WTC responders compared with non-WTC-associated thyroid cancers.

Materials and methods

Selection and enrollment of study participants

WTC responders enrolled in the World Trade Center Health Program (WTCHP) at Mount Sinai Hospital prior to their cancer diagnosis were eligible to enroll in the WTC Biobank (15). Thyroid cancer diagnosis was validated through linkage with the cancer registries of New York, New Jersey, Pennsylvania and Connecticut, as these states accounted for 98% of the responder's residencies at time of WTCHP enrollment. The full methodology of patient recruitment and consenting has been described previously (15). In summary, eligible patients were contacted by phone and then mailed a consent form if interested in participating. After obtaining consent, a cancer tissue sample was obtained from the hospital where the patient received thyroid cancer surgery and stored in the WTC Biobank, together with de-identified demographic and clinical data. For the current study, 30 eligible WTC thyroid cancer patients were identified in the WTC Biobank and frequency matched by sex, age at diagnosis (±5 years), race and histology to 30 non-WTC thyroid cancer patients from the Mount Sinai Cancer Biorepository (16). The study was conducted under the approval of the Icahn School of Medicine at Mount Sinai´s Institutional Review Board (IRB-17-01323).

The following variables were collected for all WTC and non-WTC thyroid cancer patients: age at diagnosis, sex, histology, tumor size, extrathyroidal extension, vascular invasion, presence of lymph nodes measuring >3 cm, presence of more than five lymph nodes measuring 0.2–3 cm, TNM stage and American Joint Committee on Cancer (AJCC) staging (8th edition) (17,18). Following the 2015 American Thyroid Association Management Guidelines, thyroid cancers were stratified into low (intrathyroidal differentiated thyroid cancer, ≤5 lymph node micrometastasis (<0.2 cm), intermediate (aggressive histology, minor extrathyroidal extension, vascular invasion or >5 involved lymph nodes (0.2–3 cm) and high risk (gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph node >3 cm) (19).

Macrodissection and DNA isolation

After sample de-identification, formalin-fixed paraffin-embedded tissue samples (4 µm) of the 60 patients were sent to John Hopkins University for analysis, as described previously (8). For each patient, whose slides were accessible, areas of interest were circled on a hematoxylin and eosin (H&E)-stained slide by an expert pathologist and the corresponding areas from extra slides were manually macrodissected using a razor blade, to remove contaminating normal cells. The tissue fragments were placed in a 1.5 ml microcentrifuge tube, deparaffinized with xylene, vortexed and centrifuged at 14 000 rpm × 5 min. The tissue pellet was washed twice with 100% ethanol and centrifuged for 3 min at 20 000*g*. The DNA was extracted using the kit Gene Read DNA FFPE tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions and quantified using a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

Detection of *BRAF V600E* mutation

To detect the *BRAF V600E* mutation, TaqMan Mutation Detection Assays (Thermo Fisher Scientific), a competitive allele-specific assay which reliably discriminate the *BRAF V600E* (Hs00000111_mu) and BRAF wild-type (Hs00000110_wt), was used. PCR (polymerase chain reaction) was performed in a 20 µl final volume containing 20 ng of DNA, 1× TaqMan Genotyping Master Mix and 1× TaqMan BRAF assay (*BRAF V600E* or wild-type). PCR

reaction was performed in QuantStudio 12K Flex Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific), with following cycling condition: 95°C for 10 min, 5 cycles of 92°C for 5 s and 58°C for 1 min and 40 cycles of 92°vC for 15 s and 60°C for 1 min. The analysis was according to the manufacturer's instructions.

Detection of TERT promoter mutations

The most prevalent *TERT* promoter mutations (C250T or C228T) were assessed using two TaqMan SNP (single-nucleotide polymorphism) genotyping assays (Hs000000092_rm and Hs000000093_rm), which reliably discriminate the mutant from the wild-type alleles (Cat#A44177; Thermo Fisher Scientific), as described previously (20). Briefly, the PCR reaction for each assay consisted of 30 ng of DNA, 1× TaqMan Genotyping Master Mix and 1× Custom TaqMan *TERT* mutation assay (C228T or C250T) and run on QuantStudio 12K Flex Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific). *TERT* promoter mutation was considered present when either C250T or C228T mutation was present or both.

Statistical analysis

Continuous variables were summarized using mean ± standard deviation, whereas categorical variables were summarized as frequency (%). To compare the clinical and pathological features between the WTC and non-WTC thyroid cancer groups, two-sided *t*-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables were performed.

Unadjusted logistic regression modeling was conducted to compare *BRAF V600E* status and *TERT* status between WTC thyroid cancers and non-WTC thyroid cancers, followed by adjusted logistic regression modeling adjusting for age, sex, race (White and non-White) histology and tumor size. The interaction between *BRAF V600E* status and *TERT* status was explored.

All statistics presented here were done using SAS 9.4 (SAS Institute, Cary, NC).

Results

Of the 60 thyroid cancers tissue samples sent for DNA extraction, 17 (10 WTC and 7 non-WTC thyroid cancers) did not contain enough material or DNA was degraded thus leaving 20 WTC thyroid cancers and 23 non-WTC thyroid cancers to be included in the analysis. Of the 10 WTC cases excluded from this analysis because of lack of DNA, 2 were follicular thyroid carcinoma and 1 was oncocytic thyroid carcinoma and vascular/capsular invasion was observed, no vascular invasion was observed in 3 papillary cases; information was not available from the pathology report for 3 cases and the pathology report was missing for 1 case. In the non-exposed group, vascular invasion was only noted for 1 follicular thyroid carcinoma case.

There was no difference in age ($P = 0.880$), sex ($P = 0.486$), histology ($P = 0.331$) and tumor size ($P = 0.376$) between the two groups (Table 1). Although vascular invasion was significantly more present in the WTC than non-WTC thyroid cancer group ($P = 0.038$), there was no significant difference in risk stratification ($P = 0.295$). No significant difference in the presence of *BRAF* V600E mutation was found between the two groups, although the frequency was slightly higher in the WTC than in the non-WTC thyroid cancer group, with 15 patients (75%) and 14 patients (60.9%) having this mutation, respectively ($P = 0.324$). A *TERT* promoter mutation was significantly more prevalent in WTC thyroid cancers (70%; 14/20) compared with non-WTC thyroid cancer patients (34.8%; 8/23) ($P = 0.021$). The C250T *TERT* mutation was far more prevalent (83%; 19/23) than C228T *TERT* mutation (17%; 4/23). The presence of combined mutations was not significantly different between the two groups ($P = 0.058$) (Table 1).

Although no difference in the presence of *BRAF V600E* mutation was found between WTC and non-WTC-exposed thyroid cancers [OR: 1.93 (95% CI: 0.52–7.17)], the odds of a *TERT* promoter mutation was significantly greater in the WTC versus the non-WTC thyroid cancer group [OR: 4.38 (95% CI: 1.21–15.81)]. After adjustment, the odds of *TERT* promoter mutation remained significantly greater in the WTC versus the non-WTC thyroid cancer group [OR_{adj}: 7.11 (95% CI: 1.21–41.83)] (Table 2). There was no interaction between *BRAF V600E* and *TERT* promoter mutations ($P = 1.00$).

Discussion

This mutational analysis of thyroid cancers developed following exposure to a mixture of pollutants present in the dust cloud following the WTC disaster provides the first evidence that *TERT* promoter mutations are more prevalent in these cancers compared with non-WTC-exposed thyroid cancers, potentially indicating a pathway responsible for the excess in thyroid cancer risk found in WTC-exposed populations (1–4).

BRAF V600E mutations are the most commonly found genetic alterations in adult papillary thyroid cancer, ranging between 27 and 83% (21). Analysis of 500 adult papillary thyroid cancers in The Cancer Genome Atlas (TCGA) found that a *BRAF* V600E mutation was present in 59.7% of the cancers (22). The *BRAF* gene is a member of the RAF family of serine/threonine protein kinases, which have an important role in cell proliferation, differentiation and programmed cell death (23). Because RAF proteins activate the mitogen-activated protein kinase pathway, inappropriate activation of the mitogen-activated protein kinase pathway following a *BRAF* mutation may result in abnormal proliferation and differentiation (21,23). It has been shown that activation of these pathways is predominantly implicated in the pathogenesis of papillary thyroid cancer, and associated with high-risk clinicopathological characteristics and thus thyroid cancer aggressiveness in adults (24,25). In present study, 96% of included thyroid cancers had papillary histology. It is therefore not surprising that both groups had high prevalence of *BRAF V600E* mutations, 75 and 61% for the WTC and the non-WTC thyroid cancer group, respectively.

Telomerase reverse transcriptase (TERT), a subunit of the catalytic core of human telomerase, controls the activity of telomerase. Although telomerase is responsible for elongation of the telomeric DNA, it can also lead to infinite malignant cell proliferation by stabilizing the telomere length. *TERT* promoter mutations, which have been associated with reactivation of TERT RNA expression, have been associated with cancer progression as it enhances cell proliferation (26). Two *TERT* promoter mutations of interest, namely chr5:1,295,228C>T (C228T) and chr5:1,295,250C>T (C250T), were found to be prevalent in aggressive thyroid cancers, including tall

Table 1. Characteristics of study participants

	WTC thyroid cancers (n = 20)	Non-WTC thyroid cancers (n = 23)	P value
Age at diagnosis (years)	47.4 (±7.1)	46.9 (±11.4)	0.880
Sex, n (%)			0.486
Male	15 (75)	15 (65.2)	
Female	5 (25)	8 (34.8)	
Race, n (%)			0.272
White	11 (55)	17 (73.9)	
Black	2 (10)	3 (13)	
Hispanic	1 (5)	1 (4.3)	
Asian/Pacific Islander	1 (5)	2 (8.7)	
Multiracial	2 (10)	0 (0)	
Unknown	3 (15)	0 (0)	
Histology, n (%)			0.331
FTC	0 (0)	1 (4.35)	
FVPTC	3 (15)	6 (26.1)	
Micro PTC	4 (20)	1 (4.35)	
PTC	13 (65)	15 (65.2)	
Tumor size[a] (cm)	1.58 (± 0.99)	1.34 (± 0.74)	0.376
Extrathyroidal extension, n (%)[b]			0.661
0	12 (63.2)	16 (69.6)	
1	7 (36.8)	7 (30.4)	
Vascular invasion, n (%)[a]			**0.038**
0	15 (78.9)	22 (100)	
1	4 (21.1)	0 (0)	
Lymph nodes >3 cm			0.092
0	17 (85.0)	23 (100)	
1	3 (15.0)	0	
More than five lymph nodes of 0.2–3 cm			0.440
0	15 (75.0)	20 (87.0)	
1	5 (25.0)	3 (13.0)	
ATA Risk Stratification[d]			0.295
Low	10 (50.0)	16 (69.6)	
Intermediate	2 (10.0)	3 (13.0)	
High	8 (40.0)	4 (17.4)	
T-stage[a], n (%)			0.909
1	10 (55.5)	14 (60.9)	
2	5 (27.8)	5 (21.7)	
3	3 (16.7)	4 (17.4)	
N-stage[c], n (%)			0.281
0	1 (7.7)	3 (30.0)	
1	12 (92.3)	7 (70.0)	
AJCC staging[b], n (%)			1.000
I	16 (84.2)	20 (87.0)	
II and III	3 (15.8)	3 (13.0)	
BRAF V600E mutation, n (%)			0.324
No	5 (25.0)	9 (39.1)	
Yes	15 (75.0)	14 (60.9)	
TERT promoter mutation, n (%)			**0.021**
No	6 (30.0)	15 (65.2)	
Yes	14 (70.0)	8 (34.8)	
Combined mutations, n (%)			0.058
TERT and *BRAF V600E* WT	1 (5)	5 (21.7)	
1 WT and 1 mutation	9 (45)	14 (60.9)	
TERT and *BRAF V600E* mutation	10 (50)	4 (17.4)	

FTC, follicular thyroid carcinoma; FVPTC, papillary thyroid carcinoma, follicular subtype; PTC, papillary thyroid carcinoma; WT, wild-type.
[a]Two missing tumor size; T stage; vascular invasion.
[b]One missing AJCC staging/extrathyroidal extension.
[c]20 N stage missing.
[d]Following the 2015 American Thyroid Association Management Guidelines, thyroid cancers were stratified into low (intrathyroidal differentiated thyroid cancer, ≤5 lymph node micrometastasis (<0.2 cm), intermediate (aggressive histology, minor extrathyroidal extension, vascular invasion or >5 involved lymph nodes (0.2–3 cm) and high risk (gross extrathyroidal extension, incomplete tumor resection, distant metastases, lymph node >3 cm, TERT or TERT + BRAF V600E mutation). The results in bold are statistically significant.

Table 2. Association of the presence of BRAF V600E or TERT promoter mutations in WTC thyroid cancers versus non-WTC thyroid cancers

	Unadjusted analysis OR (95% CI)	Adjusted analysis[a] OR_{adj} (95% CI)
BRAF V600E mutation	1.93 (0.52–7.17)	1.12 (0.23–5.48)
TERT promoter mutation	**4.38 (1.21–15.81)**	**7.11 (1.21–41.83)**

[a]Adjusted for age at diagnosis, sex, race, histology and tumor size. The results in bold are statistically significant.

cell papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer and *BRAF*-positive papillary thyroid cancer (27). Although an association between *TERT* promoter mutation and vascular invasion has been suggested, two recent meta-analyses did not confirm this association: pooled OR: 1.78 (95% CI: 0.83–3.84) and pooled OR: 1.38 (95% CI: 0.84–3.33) (28,29). *TERT* inhibition in two PTC carcinoma cells (BCPAP and TPC1) decreased cell invasion, migration and angiogenesis. The author suggested that BIBR1532 (*TERT*-specific inhibitor) and *TERT* siRNA significantly repress *TERT* expression and reduce PTC cell invasion, migration and angiogenesis by downregulating *TERT* target gene expression such as MMP-2, MMP-9 and VEGF. Additionally, *TERT* inhibited angiogenesis in these PTC cells, explaining, at least in part the clinical observation (30). Present study is the first to describe an increased prevalence of *TERT* promoter mutations in WTC-exposed thyroid cancers, which may partially explain the thyroid cancer risk excess found in this population because of *TERT* mutation-associated aggressive cancers (31).

WTC responders have been exposed to a mixture of pollutants present in the WTC dust cloud (10,11). Although multiple of these pollutants has been classified as carcinogens, including asbestos, benzene, dioxins, chromium and polychlorinated biphenyls, research into the association between exposure to one of these pollutants and specific mutations has been limited (32). Asbestos exposure may potentially be associated with *TERT* promoter mutations as this mutation has been identified in malignant pleural mesothelioma, an aggressive tumor arising from the pleural cavities with as major risk factor past exposure to asbestos (33). Another hypothesis is that *TERT* overexpression may play a non-canonical role in cancer, which includes inflammatory response, activation of pro-cancer genes expression, reactive oxygen species generation, invasion and metastasis (34,35). Further analysis needs to better understand the role of *TERT* promoter mutation in WTC-exposed thyroid cancer cases.

Our study has several limitations. The sample size of the WTC-exposed thyroid cancer group was initially limited to 30 patients with samples stored in the WTC Biobank, and then further reduced to 20 patients due to lack of degraded tumor DNA following DNA extraction, reducing the power to detect a difference. This study only focused on *BRAF V600E* and *TERT* promoter mutations. Future analyses of this uniquely exposed cohort of thyroid cancer patients warrants inclusion of *RAS* mutations, DNA fusions and strand breaks, as well as combinations of different mutations as potential causes of the excess thyroid cancer risk. Additionally, investigation of mutational signatures of WTC dust pollutants would be of interest.

In conclusion, the increased prevalence of *TERT* promoter mutations in the WTC-exposed thyroid cancer may indicate that exposure to the mixture of pollutants present in the WTC dust cloud following the 9/11 disaster resulted in an excess thyroid cancer risk and potentially more aggressive thyroid cancer. This result warrants questioning WTC responders about potential thyroid-associated symptoms as well as physical examination of the thyroid gland during the yearly screening visits. Future studies should also include long-term follow-up of the WTC-exposed thyroid cancer cohort to provide important insights in whether thyroid cancer-specific survival is negatively affected by exposure to the WTC dust cloud pollutants, potentially because of the presence of one or more driver mutations.

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Data availability

The data that support the findings of this study are available from the senior author, E.T., upon reasonable request.

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