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Short Report

Excess HPV-related head and neck cancer in the world trade center health program general responder cohort

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The World Trade Center (WTC) attacks exposed rescue and recovery workers to a complex mix of toxicants, including carcinogens. our study compared site-specific cancer incidence of head and neck cancers (HNC) from 2003 through 2012 among 33,809 consented WTC General Responder Cohort (GRC) members to the New Jersey State Cancer Registry, using standardized incidence ratios (SIRs). HNC grouped using SEER ICD-O-3 codes into HPV-related (oropharyngeal) and non-related (other oral-nasal; laryngeal) tumors based on anatomical site. For the 73 GRC members identified with HNC, proportional hazard regression assessed the relationship between WTC exposure and other socio-demographic characteristics. An overall excess of HNC was not observed (SIR = 1.00, 95% CI: 0.78, 1.25) but excess cancer was seen in the latest observation period (2009–2012: SIR = 1.4; 95% CI: 1.01, 1.89). A similar temporal pattern was seen for HPV-related oropharyngeal cancer and laryngeal cancer, but not for non-HPV-related sites (oral-nasal cancer). HNC was significantly associated with increasing age (8% per year, 95% CI: 5%, 12%), non-Hispanic white ethnic group-ethnicity (hazard ratio (HR) = 3.51, 95 CI: 1.49, 8.27); there was a borderline association with the 9/11 occupation of military/protective services *vs.* others (HR = 1.83 95% CI: 0.99, 3.38; $p = 0.0504$). Caution is needed in interpreting these results given the small number of cases, potential for surveillance bias, and long latency for most cancers. Our findings highlight the need to examine the potentially carcinogenic effects of WTC exposure in the context of other strong risk factors, and the need for continued medical monitoring of WTC responders.

Introduction

The attacks of September 11, 2001 (9/11) on the World Trade Center (WTC) exposed those involved in the rescue, recovery, and clean-up efforts to a complex mix of toxicants. Exposures ranged from acute immersion in the dust cloud on 9/11[1] to chronic exposures that extended into the summer of 2002.[2–4] In response to concerns about these exposures, the WTC Health Program (WTCHP) began in July 2002 and continues

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What's new?

Persons involved in rescue, recovery, and clean-up efforts associated with the September 11, 2001, attacks on the World Trade Center (WTC) in New York City were exposed to numerous toxic chemicals. Within a decade of the attacks, excess cancer incidence was detected among individuals in the WTC Health Program General Responder Cohort (WTCHP GRC). The present report now describes a small but significant increase in head and neck cancer (HNC) in the WTCHP GRC, specifically in human papilloma virus (HPV)-related oropharyngeal cancer and laryngeal cancer. Whether WTC exposures are associated with increased HPV-related cancer in WTC responders, however, remains unclear.

to provide medical monitoring and treatment for health outcomes associated with WTC exposure for general responders (e.g., police and construction workers). Eligibility criteria for the WTCHP General Responder Cohort (GRC) include dates, times, duties, and locations worked during the 9/11 response. Services are provided in the WTC Clinical Centers of Excellence (CCE) of the Icahn School of Medicine at Mount Sinai, NY University School of Medicine, Northwell Health, State University of New York, Stony Brook, and Rutgers the State University of NJ.[5]

The WTC debris cloud contained many known and suspected human carcinogens, including asbestos, silica, benzene, polychlorinated biphenyls, polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), and many types of particles including wood, cement and metal dusts.[1,2,6] A significant excess of all cancers (8% to 15%) has been observed in longitudinally followed, WTC-exposed cohorts through 2011, an excess driven largely by prostate and thyroid cancers.[7–9]

These excesses were observed in longitudinally followed, and medically monitored, WTC-exposed populations and, as such, may be due to detection or selection biases.[10] However, a number of factors indicate that, for prostate cancer, the excess may not be due to surveillance bias. These include early onset and late stage of diagnosis as well as a dose–response relationship for clinical stage at diagnosis (mid-level *vs.* low exposure odds ratio (OR) = 2.43, 95 CI: 0.51, 11.64; high *vs.* low exposure OR = 5.58, 95 CI: 1.05, 29.76).[11]

A significant excess of HNC had not been previously identified among the WTC-exposed cohorts; an SIR for oropharyngeal cancer was reported in the WTCHP GRC in 2008 of 1.21 (95% CI: 0.75, 1.86).[8] However, an apparent unusually high number of head and neck cancers (HNC) among WTC-exposed patients has been reported by clinicians.[12,13] It is biologically plausible that HNC cancer incidence may be attributable to the WTC exposures for several reasons: i) the dust composition; ii) the main route of exposure being inhalation; and, iii) the high exposure intensity in the first days after the towers' collapse. The WTC dusts included materials that are strongly associated with HNC incidence in occupational settings, including dusts (e.g., wood), chemicals (e.g., formaldehyde) and fibers (e.g., asbestos).[14–17] Inhalation of WTC pollutants provided direct exposure of the oral cavity to all sizes of particles within the airborne debris. Indeed, because of the dense concentration of larger, non-respirable airborne particles in the plume, those engulfed in the debris cloud resorted to mouth-breathing, further intensifying the high exposure to the oral cavity.[18] Potential exposure continued for many months as the WTC dust remained suspended in the air for weeks and was constantly re-suspended by the ongoing recovery and cleanup work occurring on the pile, in residencies and businesses south of Canal street, and at the landfill on Staten Island where WTC-refuse was transferred.[2]

An important possible causal mechanism for WTC exposure is the potential for synergism between well-established personal risk factors for HNC incidence, including tobacco use (all HNC), heavy alcohol use (oral cavity) and persistence of oral infection with the human papilloma virus (HPV) (oropharyngeal (OP) tonsil and base of the tongue). Synergistic interactions have been observed between occupational exposures and some modifiable risk factors (e.g., tobacco and asbestos)[19] and are considered important potential pathways in the etiology of WTC-related cancers.[20] Chronic inflammation of the upper respiratory tract, a common sequelae of WTC exposure, is a potential pathway that may promote persistence of HPV infection in the oropharynx.

To estimate the risk of HNC in the WTCHP GRC, we examined site-specific incidence of HPV-associated and non-HPV-associated HNC in three time periods from 2003 through 2012, comparing HNC incidence among the WTCHP GRC to contemporaneous HNC incidence among cases reported to the New Jersey State Cancer Registry.

Materials and Methods

Study population—the WTC health program general responder cohort

The WTCHP GRC has been previously described. Briefly, the WTCHP GRC is an open cohort that began enrollment in 2002. It includes workers and volunteers who were part of the rescue and recovery effort that followed the 9/11 attacks on the WTC in New York City. (Fire Department of New York City responders are not included in this cohort but are covered by another program within the WTCHP.) Members are eligible for annual routine monitoring visits that include: interview-administered questionnaires about physical and mental health and WTC exposure (at first visit); a physical examination; and relevant laboratory testing. Treatment is provided for WTC-related diagnoses, including cancer. Participants are asked to consent so that their data can be aggregated and included in any research.[5]

Data from the WTCHP GRC are managed by the WTC General Responder Data Center (GRDC) at the Icahn School of Medicine at Mount Sinai. The GRDC routinely conducts linkages with the National Death Index (NDI) and population-based cancer registries in New York, New Jersey, Connecticut, Pennsylvania, Florida, and North Carolina to ascertain new, and to confirm self-reported, cancer diagnoses among the cohort. After establishing a Data Use Agreement with the GRDC and obtaining approval from the Rutgers, the State University of New Jersey Institutional Review Board, we obtained de-identified data for 35,087 WTCHP GRC members with and without head and neck cancers. The information obtained included: the study participants' sex; birth year; WTCHP enrollment date; education level; ethnic group-ethnicity (white, other); smoking status (ever, former, never); 9/11 occupation/function on the recovery effort (construction, protective services/military, other/unemployed/retired); cancer anatomical site (ICD-O-3 codes), year of cancer diagnosis, and WTC exposure classification (low, medium, high, and very high, as previously described by Wisnivesky[21]; because of the small number of cases in the latter category, we combined the two highest levels into high/very high.) For responders with HNC, information was also provided about whether the diagnosis occurred more than 6 months after WTCHP GRC enrollment.

HNC was defined using standard SEER ICD-O-3 codes and grouped into HPV-related and non-related sites based on those described by Brown *et al.* (2012; Supporting Information Table 1). We compared cancer incidence using standardized incidence ratios (SIRs) computed as the ratio of observed-to-expected cancer cases, stratified into 3 cancer-site categories: (1) HPV-related (base of tongue and tonsillar); (2) other oral cavity, nasal and nasal sinuses, and (3) laryngeal. We also stratified by calendar period (2003–2008, 2009–2012). We used age-, sex-, ethnic group-, and year of specific NJ State cancer rates to calculate expected cases. To assess the possible impact of self-selection into the cohort based on symptoms, SIRs were recalculated after excluding cancers and person-years of people diagnosed within six months of enrollment into the WTCHP GRC or earlier. This analysis was conducted only for the entire sample (2003–2012) due to sample size limitations.

Cox proportional hazard regression was used to assess factors independently associated with HNC in the WTCHP GRC. Variables of interest included WTC exposure (reference level = low), patient age on 9/11/2001, sex (reference = female); ethnic group/ethnicity (reference = other); education level (reference = ≤ high school graduate); cigarette smoking (ever, reference = never); and, occupation on 9/10/2001 (protective services/military, reference = all others). We assessed the validity of the proportional hazards assumption by testing for interaction between follow-up time and WTC exposure. Analyses were conducted using SAS/STAT software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

The 73 GRC members with a diagnosis of HNC from January 1, 2003 to the date of last NJ cancer registry match (December 31, 2012) were on average older than other GRC members, with 15.1% of cases age 55 or older, compared to 5.3% of the GRC members ($p < 0.001$, Table 1.) Compared to all GRC members, a higher proportion of GRC members with HNC were male ($p = 0.037$), white compared to other ethnic group/ethnic groups ($p < 0.001$), and reported ever smoking ($p = 0.042$). There was no significant difference in the distribution of occupation or WTC exposure level between responders with and without HNC.

Over the study period (2003–2012), an overall excess of HNC compared to the age- and sex-similar population of NJ was not observed (SIR 1.00, 95% CI: 0.78, 1.25; Table 2); however there was a significant 40% elevation in the latest observation period (2009–2012: 95% CI 1.01, 1.89). This pattern was observed for HPV-related OP cancer sites and laryngeal cancer but not for non-HPV-related sites. When restricted to the cancers diagnosed more than 6 months after enrollment, the findings for all were attenuated (Table 2).

In Cox proportional hazard models, we saw a positive and significant association with head and neck cancer and increasing age (8% per year, 95% CI 5%, 12%; Table 3) and with non-Hispanic white ethnic group-ethnicity (HR 3.51, 95 CI 1.49, 8.27). We saw a borderline statistically significant association with being in the military or protective services during the 9/11 recovery effort (1.83 95% CI 0.99, 3.38; $p = 0.0504$). Given the similar distribution among cases and non-cases, this latter observation was not expected, so we explored the joint distribution of this variable with other factors in bivariate analysis. Within all levels of age, we saw a strong relationship with age, such that a higher percentage of older cases worked in protective services compared to those who did not have HNC. We thus explored the joint effect of age at 9/11 and occupation by including an interaction term in the model. However, this term was not statistically significant ($p = 0.1560$) nor was the inclusion of the interaction term effective in improving the model fit (using the likelihood ratio test); therefore, the term was not included in the final model.

Discussion

We observed a small, positive but significant excess of cancers of the head and neck among WTCHP GRC from 2009 through 2012. This excess was seen among oropharyngeal cancer (SIR = 1.73, 95% CI: 1.02, 2.73) and laryngeal cancer (SIR = 1.83, 95% CI: 0.97, 3.13) but was not seen among oral and nasal cancer sites (SIR = 0.85, 95% CI: 0.41, 1.56). To our knowledge, an excess of HNC has not been previously reported in WTC-exposed populations. However, the usual positive prognostic impact of HPV infection has been observed to be mitigated among patients with WTC exposure. This report differs from previous reports of cancer excess in

Table 1. Characteristics of World Trade Center Health Program General Responder Cohort (WTCHP GRC) members with and without cancer of the head and neck; 2003–2012

	WTC HNC Cases (n = 73)		WTCHP GRC (n = 33,809)		
	n	%	n	%	*p*-Value
Age at 9/11 (n = 67)					
25 to 44	38	(52.1)	25,579	(75.7)	
45 to 54	24	(32.9)	6,454	(19.1)	
≥55	11	(15.1)	1,776	(5.3)	‹0.001
Sex					
Male	[1]	(›95.0)	30,139	(85.9)	
Female	[1]	[1]	4,948	(14.1)	0.037~
Ethnic group/ethnicity					
White	59	(88.1)	19,922	(65.1)	
Other	8	(11.9)	10,669	(34.9)	‹0.001
Smoking status					
Current	11	(15.7)	4,871	(14.3)	
Former	27	(38.6)	8,680	(25.5)	
Never	32	(45.7)	20,426	(60.1)	0.063
Educational level					
≤HS Grad	30	(41.1)	9,848	(29.3)	
Some college	23	(31.5)	13,832	(41.2)	
BA/BS or higher degree	20	(27.4)	9,893	(29.5)	0.051
Lifetime occupation					
Construction	18	(24.7)	6,642	(19.8)	
Protective Services/Military	33	(45.2)	17,473	(52.1)	
Other/Unemployed/Retired	22	(30.1)	9,434	(28.1)	0.488
WTC exposure group[1]					
Low	10	(14.5)	5,360	(16.0)	
Intermediate	46	(66.7)	21,108	(62.9)	
High or Very high	13	(18.8)	7,084	(21.1)	0.826

[1]Cells counts of ‹5 are suppressed under the terms of the data use agreement with the WTC Health Program Data Center.
[2]Yates corrected Chi-square.

this cohort in three ways: by evaluating laryngeal cancer in the grouping with HNC; by extending follow-up to 2012; and, by classifying naso-oro-pharyngeal cancer sites into those that are and are not associated with HPV infection. The increased risk in the later observation period (2009 to 2012) is consistent with a possible role for WTC exposure in carcinogenesis given the latency of many solid tumors.

While we did not observe an association between WTC dust exposure and HNC, this does not preclude a combined role for HPV infection and WTC exposure in HNC carcinogenesis. While oral HPV infection is common in US adults, carcinogenesis requires persistent HPV infection, which is less common.[22] HPV-positive OP tumors are etiologically distinct, with a different molecular and risk factor profile from HPV-negative OP tumors. The risk factor profile for patients with HPV-positive OP tumors includes a lower prevalence of cigarette and alcohol consumption.[23] In the general population, HPV infection is a strong positive prognostic indicator for OP cancer patients, associated with lower morbidity and mortality.[24] A review of 87 patients with OP cancer found that among HPV-positive OP patients, WTC-exposed patients experienced significantly poorer outcomes compared to non-WTC exposed patients (48 month disease-free survival after 4 years: 65.6% *vs.* 80.1%, respectively, $p < 0.04$).[13]

It is plausible that the baseline level of WTC exposure was sufficient to increase cancer risk in the presence of HPV infection, and further exposure in the highly exposed group did not further increase risk. One possible pathway for HNC is that WTC dust exposure could facilitate the HPV infection and persistence initially *via* direct tissue damage and then by inflammation. In mouse models, WTC dust-exposure induces inflammation and oxidative stress associated with epigenetic modifications in the lung that result in altered pulmonary mechanics.[25] WTC responders continue to have a high burden of inflammation-inducing, upper aerodigestive-tract conditions today.[26]

Carcinogenesis is a complex, multifactorial, progressive process involving the interaction of genetic and environmental

Table 2. Standardized incidence ratios (SIR) for head and neck cancer sites, stratified by HPV-related/infected by the human papilloma virus (HPV) for all WTCHP GRC members and those diagnosed ≥6 months after enrollment

	All									Diagnosed ≥6 months after enrollment		
	2003–2012			2003–2008			2009–2012			2003–2012		
Cancer site	Obs.	SIR[1]	95% CI	Obs.	SIR[1]	95% CI	Obs.	SIR[1]	95% CI	Obs.	SIR[1]	95% CI
All	73	1.00	(0.78, 1.25)	32	0.73	(0.51, 1.02)	41	1.40	(1.01, 1.89)	35	0.49	(0.34, 0.68)
Oropharyngeal	32	1.23	(0.84, 1.73)	14	0.90	(0.49, 1.50)	18	1.73	(1.02, 2.73)	12	0.46	(0.24, 0.80)
Other oral-nasal	21	0.71	(0.44, 0.09)	11	0.62	(0.31, 1.11)	10	0.85	(0.41, 1.56)	8	0.27	(0.12, 0.53)
Laryngeal	20	1.13	(0.69, 1.74)	7	0.66	(0.26, 1.35)	13	1.83	(0.97, 3.13)	15	0.84	(0.47, 1.39)

[1]The number of expected cases was calculated based on age-, sex-, ethnic group-, and year-specific NJ State cancer rates from the New Jersey State Cancer Registry.

factors, as well as epigenetic changes. Among WTC responders who have other chronic carcinogenic exposures (e.g., smoking, alcohol use, or oral HPV infection), the resulting chronic inflammation could impede appropriate repair mechanisms (for example, by p53 disruption, a mechanism common to tobacco exposure and HPV infection), and mutated cells would proliferate. In the case of HPV infection, chronic inflammatory processes that impair local immune responses can cause elevation of inflammatory cytokines, thought to influence HPV infection and persistence.[27] An analogous role for cigarette smoking mediating subsequent HPV-16 cervical infection was reported in a cohort of 1,976 US women, for whom smoking increased the risk of a subsequent infection by reducing immunity. Current- compared to never-smokers had increased odds of HPV-16 infection (odds ratio, OR: 1.29; 95% CI: 1.11, 1.73). The observed direct effect was imprecise (OR: 0.57; 95% CI: 0.26, 1.13), but a stronger indirect effect was seen among women who smoked at least half a pack daily (OR: 1.61, 95% CI: 1.27, 2.15) compared to women who smoked less (OR: 1.09; 95% CI: 0.94–1.44). This mediation hypothesis is consistent with a general model of cancer causality, whereby environmental insults disrupt the stability of the epigenome in normal cells, leading to the development of a wide range of pathologies, including cancer.[28,29]

Like all observational studies, our study has a number of limitations that should be considered when interpreting the results. Our assignment of cancer HPV-relatedness into three anatomical groups (OP, other oral and nasal, laryngeal) likely introduced misclassification, as not all oropharyngeal cancers are HPV-related, and other OP sites, as well as some percent of laryngeal cancers and oral-nasal cancer, may be HPV-related. Using the National Cancer Data Base, a study of nasopharyngeal cancer 956 found that 32% of the tumors had tested HPV-positive. This misclassification would have obscured differences between groups, and, as such, any bias introduced would be toward the null hypothesis of no difference of cancer excess among the three groups. For our SIR analysis, the expected number of HNC cases was obtained by incidence data from the New Jersey State Cancer Registry, while other reports of WTC cancer excess from the WTC GRC used incidence data from the Surveillance Epidemiology and End Reports Registry (SEER) New York and New Jersey registries.[8] While the response to the WTC attacks was a national effort, the majority of responders were from these two states. Incidence rates of HNC are similar in New York and New Jersey states, and the populations are large enough that this choice of referent should not impact the comparability with previous reports. A further limitation to using either NY or NJ population-based cancer registries for calculating expected cancer rates is that these registries likely include persons involved in the 9/11 response, or who were otherwise exposed to the events and subsequent pollution and trauma of the 9/11 attacks. If exposure to the WTC response is causally associated with cancer incidence, then this would bias the finding toward the null hypothesis.

The observed excess of cancer in this cohort may be the result of surveillance (detection) bias, as participation in this medical monitoring program may lead to cancer diagnosis in the cohort earlier than in the general population. In a case series of 16 HNC patients in this cohort, half were diagnosed

Table 3. The association between risk factors and head and neck cancers (n = 73) in Cox proportional hazard models

	Hazard Ratio	95% CI	p-value
Age on 9/11	1.08	(1.05, 1.12)	‹0.0001
Male sex (ref = female)	2.94	(0.70,12.20)	0.1404
Education (ref = ≤ high school)			
Some college	0.63	(0.33, 1.17)	0.1438
≥ 4-year college degree	0.57	(0.28, 1.17)	0.1273
Ethnic group ethnicity (ref = Other)			
Non-Hispanic White	3.51	(1.49, 8.27)	0.0041
Smoking at first visit (ref = never)			
Former	1.23	(0.67, 2.27)	0.5019
Current	1.46	(0.68, 3.12)	0.3276
Lifetime occupation (ref = other)			
Protective services/military	1.83	(0.99, 3.38)	0.0540
WTC exposure (ref = low)			
Intermediate	1.57	(0.66, 3.72)	0.3039
High or Very High	1.14	(0.41, 3.16)	0.8015

after the patient noticed symptoms and half by a clinician. The WTCHP GRC is a voluntary, open enrollment cohort. As such, self-selection into the program based on symptoms may also introduce surveillance bias.[10] Our sensitivity analysis to assess the impact of any such bias, by restricting the analysis to those enrolled six months or more after their cancer diagnosis, was underpowered, making the null results inconclusive. Other selection biases, such as the healthy worker effect, however would exert a downward bias on our findings.

The lack of association with smoking in the multivariable regression analysis was surprising, given that cigarette smoking is a strong population risk factor for HNC. However, HPV causes an epidemiologically and clinically distinct form of OP squamous cell carcinoma with risk factors related to sexual behavior, whereas HPV-negative cancers are strongly associated with tobacco and alcohol use, so the lack of association may reflect our inability to separately explore risk factors among HPV and non-HPV related HNC.[23] In addition, we did not control for drinking alcohol in this preliminary exploration. Alcohol consumption is also a strong population risk factor for non-HPV associated HNC, and future analyses should assess, to the extent possible, heavy alcohol consumption within the WTCHP data.

Sequelae from HNC and its treatment can be debilitating and include depression, facial disfigurement and speech limitations. WTC responders are at increased risk for mental health disorders including PTSD, independent of other medical conditions. If WTC exposure does increase risk for HNC, then prevention, early detection and treatment are critical to limiting the associated morbidity and mortality. Studies that enumerate the risk-factor profile for these cancers among WTC-exposed populations, and explore mediation and synergism between WTC exposure and modifiable risk factors such as tobacco and alcohol use, are important for prevention and control. The potentially carcinogenic effects of exposure to the complex mixture of substances from the WTC should be explored in the context of other strong population risk factors. The WTCHP is an essential resource for understanding the complex long-term health impacts of the 9/11 attacks.

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