Cancer risk among World Trade Center rescue and recovery workers: A review

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Abstract: Twenty years after the September 11th, 2001 terrorist attacks, the association between exposures present at the World Trade Center (WTC) site and the risk of several specific types of cancer has been reported among rescue and recovery workers. The authors' objective was to conduct an updated review of these data. Most studies have found elevated rates of both prostate and thyroid cancers compared with rates in the general population, and some have reported statistically significant differences for the rates of all cancers as well. Studies including a larger combined cohort of WTC-exposed rescue and recovery workers from 3 main cohorts have since replicated findings for these cancers, with additional years of follow-up. Among this combined cohort, although a lower-than-expected standardized incidence ratio for all cancers was observed, WTC exposure was also related to an increased risk of cutaneous melanoma and tonsil cancer. Importantly, another study found that WTC-exposed rescue and recovery workers who are enrolled in the federally funded medical monitoring and treatment program experienced improved survival post-cancer diagnosis compared with New York state patients with cancer. On the basis of these combined cohort studies, the full effect of WTC exposure on cancer risk is becoming clearer. Consequently, the authors believe that surveillance of those with WTC exposure should be continued, and in-depth analysis of epidemiologic, molecular, and clinical aspects of specific cancers in these workers should be pursued.

Keywords: disasters, epidemiology, neoplasm, review, September 11 terrorist attacks

Introduction

Twenty years ago, the World Trade Center (WTC) towers were destroyed during the September 11th, 2001 (9/11) terrorist attacks, and tens of thousands of first responders, other rescue and recovery workers (RRWs), and clean-up workers, as well as area workers and residents, were exposed to potential carcinogens. Concerns about possible risks of cancer in these populations arose shortly after the attacks,[1-3] but an adequate period of time needed to elapse before any effect on cancer could become detectable. Although some studies have addressed cancer risk in individuals who were living or working in the area,[4] most studies have been conducted among WTC-exposed RRWs (WTC-RRWs), a more homogeneous population. In this review, we examine the results of studies on cancer risk among WTC-RRWs, with emphasis on recent studies.

Exposure to Carcinogens After the WTC Attack

On the morning of 9/11, the collapse of the WTC towers blanketed lower Manhattan in dust and debris so thick that, for some, it was impossible to see more than a few feet ahead.[2] This WTC dust remained in the air for days, until rain in the early morning of September 14, 2001, helped suppress the dust.[5] However, despite spraying the debris pile with water where the towers once stood, dust was continually resuspended during the recovery and clean-up efforts.[2,5] In addition, fires caused by

the attack burned through December 2001, exposing WTC-RRWs to harmful smoke and gases.[2] Although air and dust samples collected days and weeks after 9/11 from locations surrounding the disaster site helped to inform which chemical agents were present during the recovery and clean-up efforts, individual-level exposure was not measured. The collected samples identified some known and suspected carcinogens: asbestos, arsenic, polycyclic aromatic hydrocarbons (such as benzo[b]fluoranthene, benzo[k]fluoranthene, and benzo[a]pyrene), polychlorinated biphenyls, polychlorinated furans, and dioxins.[1,2,5-8] The concentrations of these agents varied based on the locations and dates of sample collection.[2]

In the years after the attack, 3 main WTC-exposed cohorts of RRWs have been assembled under the auspices of the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) WTC Health Program (WTCHP): the Fire Department of the City of New York (FDNY), the General Responder Cohort (GRC), and the WTC Health Registry. Unfortunately, documentation of WTC work-related exposures was not systematically recorded and, when it was recorded, was often incomplete.[9,10] Therefore, epidemiologic research has needed to rely on self-reported exposure, which has been associated with many health conditions, including lower respiratory conditions, mental health, and cancer.[11-16] For example, studies from each of the cohorts have reported that those with the greatest exposure (ie, those arriving the morning of 9/11 and/or being caught in the dust cloud) have an elevated risk of asthma.[12,14,17] Although each cohort recorded information on WTC exposure through questionnaire, the questions varied by cohort. In the years after the attack, a WTCHP Working Group compared questions from each questionnaire and assigned comparable levels of exposures based on the various question-answer combinations.[10] This categorization has helped to enable collaboration across WTC cohorts.[18]

Published Reports on Cancer Among WTC-RRWs From Single Cohorts

Published studies of cancer outcomes in RRWs began with the FDNY cohort in 2011,[16] followed by studies in the other individual cohorts.[13,19-21] All studies have produced some consistent findings: first, each study found that incidence rates for all cancers were elevated compared with rates in the general population, although not all were statistically significant; second, each study reported elevated rates of prostate and thyroid cancer, as well as a reduced rate of lung cancer.[13,16,19-21] Studies also compared WTC-RRWs versus other occupational groups: compared with non–WTC-exposed firefighters, exposed FDNY firefighters had elevated rates of prostate cancer and thyroid cancer, but no difference was observed for these cancers among WTC-exposed police officers versus non–WTC-exposed police officers.[22-24]

Several site-specific cancer studies were also conducted. In 2009, a case series study in multiple myeloma reported on 8 patients, one-half of whom were diagnosed with cancer before age 45 years.[25] With extended follow-up, one study (including the WTC Health Registry cohort) showed that the multiple myeloma rate was elevated compared with that in the general population.[23] In addition, FDNY firefighters have been shown to have an elevated rate of the precursor disease to multiple myeloma (monoclonal gammopathy of undetermined significance) compared with the general population.[26] An analysis of 73 cases of head and neck cancer in the GRC showed no overall increased risk for this group of cancers; an excess risk was observed after 2008 for oropharyngeal and laryngeal cancers, but not for oral or nasal cancers.[27] In another analysis of GRC members, an association was reported between high WTC exposure and advanced clinical stage of prostate cancer[28]; and, in an analysis of a subset of GRC members,[29] an association was found between re-experiencing a traumatic event and prostate cancer incidence. As noted above, elevated thyroid cancer rates have also been observed,[13,16,19-21,30]; however, these rates may have been influenced by incidental detection related to medical surveillance,[30,31] with the majority of patients being asymptomatic at diagnosis. In addition, the rate of asymptomatic cancers was statistically greater than that in the general population, but the rate of symptomatic cancers was similar.[30]

In 2012, NIOSH assumed biologic plausibility to add most cancers to the list of WTCHP-covered conditions[32]; this assumption was based on results from the FDNY study[16] and preliminary findings from the other 2 cohorts, as well as relying heavily on previous knowledge of high exposure to known or suspected carcinogens found at the WTC site. Services include free cancer screening and treatment for eligible WTC-exposed responders and survivors enrolled in the WTCHP. The cancer screening includes low-dose chest computed tomography, colonoscopy, mammography, and Papanicolaou smears.[3,32] For some members, chest computed tomography screening and other tests,

such as prostate-specific antigen testing, were provided by outside funds before 2012. Members of the FDNY cohort still receive prostate-specific antigen testing through non-WTCHP funding.

The Need for the Combined Cohort of WTC-RRWs

Results from studies of the 3 main cohorts were not always consistent across studies, and elevated relative risks for specific cancer types often missed statistical significance at the α = .05 level. Specifically, whereas the 3 cohorts were consistent in the standard incidence ratios (SIRs) for prostate cancer, lung cancer, thyroid cancer, pancreatic cancer, and urinary/bladder cancer, there were differences for multiple myeloma, non-Hodgkin lymphoma, leukemia, stomach cancer, esophageal cancer, colorectal cancer, testicular cancer, kidney cancer, and cutaneous melanoma. In addition, the definition of surrogate measures for WTC exposure, methods for case ascertainment, selection of reference populations, and statistical methods differed across these studies, and some participants contributed cases to multiple cohorts. This made direct comparisons across the cohorts difficult. Furthermore, many of these findings could be affected by short follow-up and by the small numbers of cases, leading to the possibility of chance findings.

Therefore, these inconsistencies in both methodology and findings, and the overlaps in cohort membership prompted the study investigators to combine their data with consistent case definitions and ascertainment, harmonized exposure definitions, and additional follow-up.[18,33] The New York State (NYS) Cancer Registry played a crucial role in this effort by acting as the honest broker to eliminate duplicates and provide consistent outcome data. By using this combined cohort, cancer incidence and survival have been reported and represent the most informative data to date.

Published Reports on WTC-RRWs From the Combined Cohort

Cancer Incidence

The combined cohort incidence study included 57,402 WTC-RRWs who were predominantly aged 30 to 49 years as of September 11, 2001 (69.4%), mainly men (84.1%), largely non-Hispanic White (71.7%), and mostly never-smokers (59.7%). Nearly 84% of individuals in the combined cohort were enrolled between September 11, 2001, and December 31, 2004. Further description of the cohort is provided in Table 1.[34] In total, 3611 incident cancer cases were identified with follow-up through the end of 2015, of which 3236 were reported as first primary cancers, with an accumulated 649,724 and 624,620 person-years of

TABLE 1. Selected Cohort Characteristics[a]

CHARACTERISTIC	NO. (%)
Age on September 11, 2001: Mean ± SD, y	39.6 ± 9.8
Sex	
Men	48,251 (84.1)
Race/ethnicity	
Non-Hispanic White	41,130 (71.7)
Non-Hispanic Black	5614 (9.8)
Non-Hispanic American Indian/Alaska Native	160 (0.3)
Non-Hispanic Asian/Pacific Islander	1134 (2.0)
Hispanic, any race	9364 (16.3)
Smoking status at enrollment[b]	
Current	9315 (16.4)
Former	13,363 (23.5)
Never	34,264 (60.2)
Vital status by December 31, 2015	
Deceased	1714 (3.0)
WTC exposures	
Date of arrival at WTC site[c]	
September 11, 2001	20,948 (38.7)
September 12, 2001	10,595 (19.6)
September 13-17, 2001	11,143 (20.6)
Later than September 18, 2001	11,476 (21.2)
Performed tasks on pile[d]	
Yes	23,086 (40.6)
No	33,725 (59.4)
Cancer	
No. of tumors	3611
No. of distinct persons	3380 (5.8)
Top cancers diagnosed: No. of tumors/persons	
Prostate	1061/1061
% Localized	77.3
Lung and bronchus	249/241
% Localized	32.9
Cutaneous melanoma	236/229
% Localized	75.0
Colon/rectum	233/229
% Localized	44.6
Thyroid	208/207
% Localized	64.9

Abbreviations: WTC, World Trade Center.
[a]Note that some of the above data were published previously by Li et al.[34]
[b]Of the overall study population, n = 460 (0.8%) had unknown/missing information.
[c]Of the overall study population, n = 3240 (5.6%) had unknown/missing information.
[d]Of the overall study population, n = 591 (1.0%) had unknown/missing information.

follow-up, respectively.[34] Expected counts were computed by stratifying counts and person-years by age (ages 18 and 19 years, 20-84 years [in 5-year bins], and 85 years or older),

TABLE 2. Specific Cancers at Increased and Decreased Incidence in the Pooled World Trade Center Rescue and Recovery Worker Cohort Compared With the New York State Population[a]

CANCERS AT INCREASED INCIDENCE				CANCERS AT DECREASED INCIDENCE			
CANCER	NO.	SIR	95% CI	CANCER	NO.	SIR	95% CI
Prostate	1001	1.19	1.11-1.26	Lung	200	0.59	0.51-0.67
Cutaneous melanoma	204	1.43	1.24-1.64	Female breast	140	0.82	0.69-0.96
Thyroid	189	1.81	1.57-2.09	Colon	133	0.76	0.64-0.90
Tonsil	40	1.40	1.00-1.91	Bladder	130	0.81	0.67-0.96
				Rectum	79	0.76	0.60-0.95
				Pancreas	56	0.68	0.51-0.88
				Liver	54	0.64	0.48-0.83
				Endometrium	29	0.67	0.45-0.96

Abbreviations: CI, confidence interval; NO., number of observed cases; SIR, standardized incidence ratio.
[a]Note that some of these data were published previously by Li et al.[34]

sex, race/ethnicity (Hispanic/Latino, non-Hispanic White, non-Hispanic Black, American Indian-Alaska Native, and Asian/Pacific Islander), and calendar year (5-year intervals), and were indirectly standardized to NYS population rates. The SIRs were then calculated by taking the quotient of observed and expected cases. For all first primary cancers combined, the SIR was 0.96 (95% confidence interval [CI], 0.93-0.99); elevated SIRs were observed for cutaneous melanoma and for prostate, thyroid, and tonsil cancers; and reduced SIRs were observed for several digestive, respiratory, and female reproductive cancers (Table 2).[34] Nine cases of mesothelioma were observed, yielding a SIR of 1.38 (95% CI, 0.63-2.62). Thyroid cancer was elevated primarily among RRWs who were participating in medical monitoring and treatment programs, suggesting the impact of medical surveillance.[35]

In internal analyses comparing those who first worked on the WTC effort on September 11, 2001, with those who started after September 17, 2001, there was an increased risk for prostate cancer (hazard ratio [HR], 1.61; 95% CI, 1.33-1.95) and thyroid cancer (HR, 1.77; 95% CI, 1.11-2.81), with an exposure-response trend for both cancers. Self-reported exposure to the dust cloud itself was also associated with an increased risk of prostate cancer (HR, 1.30; 95% CI, 1.14-1.49), but not of other cancer sites.[35] Internal analyses were restricted to cancer sites that had significant SIRs in the primary analysis, and additional subtypes of cancer were not investigated.

Temporal trends in incidence were explored in detail for selected cancers and showed increased incidence in the overall analysis. In particular, 1120 incident prostate cancer cases in 54,394 male RRWs were diagnosed between March 12, 2002, and December 31, 2015.[36] From 2002 through 2006, no association with WTC exposure was detected; the incidence of prostate cancer was the same as that in the NYS reference population through 2006 (HR, 0.99; 95% CI, 0.83-1.19). Beginning in 2007, however, a 24% increased risk HR, 1.24 (95% CI, 1.16-1.32) was observed among these workers. Comparing those who arrived earliest at the WTC site, on the morning of September 11, 2001, or any time on September 12, 2001, with those who first arrived later, a positive, monotonic, dose-response association was observed both in the earlier period (2002-2006) and in the later period (2007-2015).

In total, 247 incident cases of cutaneous melanoma were observed among White RRWs (the numbers of cases among non-White RRWs were too small to analyze).[37] No increase in the incidence of melanoma was detected during 2002 through 2004; however, beginning in 2005, a 34% increased risk was observed compared with the NYS reference population (HR, 1.34; 95% CI, 1.18-1.52). A dose-response relationship was observed with time worked on the WTC effort. Finally, 225 thyroid cancers were identified among 224 participants.[35] Although thyroid cancer rates were approximately twice those of the NYS reference population throughout the study follow-up period (HR, 2.3; 95% CI, 2.0-2.7), we observed no change in the rate of thyroid cancer incidence.

Cancer Survival

The analyses of cancer survival were limited to cases from the NYS Cancer Registry.[24] To avoid lead-time bias, the survival analysis was started at January 1, 2005. From January 1, 2005, to December 31, 2016, there were 2037 cancer cases and 303 deaths (248 cancer-related deaths) among members of the pooled cohort who were members of the CDC/NIOSH WTC medical monitoring and treatment program (also called the WTCHP). This program, as mentioned above, offers free access to screening, diagnosis, and treatment for several cancers.[32] These cases were compared with 574,075 cancer cases and 224,040 deaths (158,645 cancer-related deaths) that occurred in NYS during the

same period. Mortality was lower among patients with cancer in the WTCHP (cancer-specific mortality: HR, 0.72; 95% CI, 0.64-0.8; all-cause mortality: HR, 0.64; 95% CI, 0.58-0.72). Specific cancers for which mortality was lower included cancers of the prostate (HR, 0.59; 95% CI, 0.42-0.84), lung (HR, 0.59; 95% CI, 0.44-0.78), colon and rectum (HR, 0.50; 95% CI, 0.32-0.76), and kidney (HR, 0.37; 95% CI, 0.17-0.82).

Mechanistic Studies

A limited number of studies exploring mechanisms of WTC-related cancers both in humans and experimental animals have been conducted to elucidate the findings of the epidemiologic studies. In an exploratory study of global methylation in blood samples collected during 2012 through 2014 from 185 WTC-RRWs, several cancer-related pathways, including the Ras, MAPK, and PI3K-Akt signaling pathways, emerged in analyses for the top-ranking genes from an epigenome-wide association study.[38] No association was detected, however, between estimated levels of exposure and epigenetic alterations.

Recently, the expression of immunologic and inflammatory genes on archived prostate tumors was analyzed comparing WTC-RRWs with non-WTC patients.[39] WTC prostate cancer cases showed significant upregulation of genes involved in DNA damage and G_2-M arrest. Cell-type enrichment analysis showed that T-helper 17 (Th17) cells, a subset of proinflammatory Th cells, were specifically upregulated in WTC patients. Those authors also performed RNA sequencing on the prostates of normal rats exposed to moderate to high doses of WTC dust using intratracheal inhalation. In the prostates of rats exposed to WTC dust, upregulation of gene transcripts of cell types involved in both adaptive immune response (dendritic cells and B cells) and inflammatory response (Th17 cells) was observed. These results complement previous data demonstrating that WTC dust-induced inflammation and oxidative stress were associated with epigenetic modifications in the lungs of mice exposed to WTC dust.[40]

A whole-genome sequencing (WGS) study of neoplasms in WTC-RRWs included 9 CD138-positive, bone marrow mononuclear samples from patients who were diagnosed with plasma cell disorders after the WTC disaster.[41] No differences were observed when comparing the driver and mutational signature landscapes in these cases with 110 previously published WGSs from 56 patients who had multiple myeloma and with the CoMMpass WGS cohort (ClinicalTrials.gov identifier, NCT01454297), including 752 WGSs. An analysis of time-related aspects of selected, single-base substitution, mutational signatures suggested that tumor-initiating chromosomal gains occurred both before and after WTC exposure.

Conclusions

This review summarizes results of the epidemiologic studies that have been conducted among WTC-RRWs and provides evidence of an increased incidence of specific types of cancers in this population. The strongest evidence concerns cancers of the prostate and thyroid and cutaneous melanoma. Although the precise etiologic underpinnings for these associations are unknown, prostate cancer and cutaneous melanoma have been reported to be related to environmental exposures common in firefighting,[7,42-44] and thyroid cancer may be associated with environmental exposures, such as polychlorinated biphenyls[45] and particulate matter.[46-49] However, the excess of these cancers might also be explained by detection bias if RRWs were followed more intensely than the population of NYS.[30,50] In an analysis by stage at diagnosis,[34] an excess incidence was observed at localized stages, but not at regional or distant stages, for cutaneous melanoma, suggesting that screening may play a role, whereas the incidence of prostate and thyroid cancers was similar at all stages, suggesting that the risk may also be increased independent of screening or surveillance bias. Several explanations can be proposed for the lower-than-expected incidence of several types of cancers. Some of these cancers are associated with lifestyle factors that may have a favorable distribution in RRWs, such as tobacco smoking, alcohol drinking, and overweight/obesity. In addition, this population may have benefitted from early and consistent access to health care through WTC health programs that were offered to eligible workers.[48,51,52] Furthermore, additional follow-up time may be necessary to identify cancers with long latency periods that are known to be associated with environmental exposures, such as lung cancer and mesothelioma. Furthermore, WTC-RRWs are predominantly White, middle-aged, gainfully employed men; these demographic characteristics may mitigate part of the detrimental effects of exposure on cancer incidence. Comparisons with other worker populations (other than firefighters) are necessary to better elucidate overall cancer risk. It is plausible that we are just starting to see the full effect of WTC exposure on cancer risk: for this reason, surveillance of these cohorts should be continued, in our opinion, and in-depth analyses of epidemiologic, molecular, and clinical aspects of specific cancers in these workers should be conducted. Finally, the results on survival after cancer diagnosis among WTC-RRWs enrolled in the CDC/NIOSH WTCHP indicate an important benefit of the program, one that may serve as a blueprint for other populations involved in environmental disasters.[24]

The results of these studies, in particular those of the combined cohort, may inform clinicians who have patients with WTC-related exposures. In addition to accessing the CDC/NIOSH WTCHP website (cdc.gov/wtc/)[53] to obtain

detailed information on the possible health effects of these exposures (both cancer and noncancer outcomes), clinicians can refer their patients to the Clinical Centers of Excellence established under the same health program (list available from the same website). ■

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