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Prostate cancer characteristics in the World Trade Center cohort, 2002-2013

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Abstract

Background—An increased incidence of prostate cancer was reported in three cohorts of World Trade Center (WTC) respondents. It is uncertain whether this increase is due to WTC-related exposures or enhanced surveillance.

Methods—Prostate cancer cases (2002-2013) were obtained from the WTC Health Program. Age, race and Gleason score distribution were compared to New York State Cancer Registry

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(NYSCR) cases from the same time period. Multivariate models were adjusted for age and race. Analyses of clinical characteristics of prostate cancer cases within the cohort were also performed, adjusting for age, race, and WTC exposure categories.

Results—WTC respondents had a prostate cancer age-standardized rate ratio of 1.65 (95% CI: 1.37, 1.93) compared to New York state; age-specific ratios were highest for ages 30-49 (2.28; 95% CI: 1.51-3.43), 70-74 (2.05; 95% CI: 1.03-4.10), and 80-84 years (5.65; 95% CI: 1.41-22.58). High WTC exposure was associated with advanced clinical stage (5.58; 95% CI: 1.05-29.76; p-trend=0.03).

Conclusions—WTC respondents continue to have higher prostate cancer rate compared to NYS as a whole. Respondents with a higher WTC exposure level may have had more advanced clinical stage of prostate cancer.

Keywords

prostate neoplasms; September 11 terrorist attacks; disasters; New York City; world trade center

INTRODUCTION

A moderate increased risk of prostate cancer has been reported in three cohorts of World Trade Center (WTC) respondents and workers.[1-3] In the analysis of World Trade Center Health Program (WTCHP) cancer incidence from 2002-2008, 82 confirmed cases of prostate cancer occurred at least six months after enrollment.[1] The corresponding number of expected cases was 66.7, resulting in a standardized incidence ratio (SIR) of 1.23 (95% confidence interval (CI): 0.98, 1.53). An increased prostate cancer incidence rate was also reported for a separate cohort of 9,853 NY firefighters: 90 cases were observed among exposed firefighters (SIR: 1.49; 95% CI: 1.20, 1.85) vs. 45 among unexposed firefighters (SIR 1.35; 95% CI: 1.01, 1.81); the ratio of the two SIRs was1.11 (95% CI: 0.77, 1.59).[2] The New York City Department of Health and Mental Hygiene reported 67 prostate cancer cases from 2007 to 2008 in a cohort of WTC respondents; SIR was 1.43 (95% CI: 1.11, 1.82).[3]

Several hypotheses have been put forth to explain the increase in prostate cancer incidence in WTC respondents. A concrete possibility is that WTC respondents are susceptible to over-diagnosis of prostate cancer due to surveillance bias, as part of enrolling in WTC health programs. However, if the clinical characteristics of these prostate cancer cases are indicative of a more aggressive form of prostate cancer among WTC exposed subjects, targeted research to determine the underlying biology of aggressive prostate cancers and the contributory role of WTC exposure would identify novel risk factors and incite mechanistic hypotheses. Despite being the leading cause of cancer among men, prostate cancer has few confirmed and well-established risk factors, apart from age, race, some genetic factors,[4, 5] and smoking.[6] There would be major clinical and preventive consequences in characterizing prostate cancer cases of WTC respondent cases and disentangling the role of WTC exposure in the observed prostate cancer increase among members of this cohort.

As it stands, the associations between clinical characteristics of prostate cancer and WTC-related exposures remains undetermined. This study aims to characterize WTC respondent prostate cancer cases and assess whether prostate cancer over-diagnosis occurred WTC respondents due to increased health surveillance. The second aim is to analyze the associations of WTC-related exposure with clinical benchmarks of prostate cancer advancement.

METHODS

Study Population

The WTCHP has been described in detail elsewhere.[7-9] Enrollment in the WTCHP has been continuous since 2002. Briefly, responders enrolled in the program between July 16, 2002 and December 31, 2013 completed examinations that included demographic, exposure assessment questionnaires, and physical examinations. The present analyses includes program participants who consented to participate in research and had a diagnosis of prostate cancer confirmed by the New York State Cancer Registry (NYSCR), registries from other US states, or cases confirmed by pathological records, and who were enrolled in one of the WTCHP's clinical sites (Icahn School of Medicine at Mount Sinai, New York University (NYU) School of Medicine, North Shore-LIJ Health System (LIJHS), State University of New York, Stony Brook, Rutgers University). The number of WTC respondents who did not consent to have their data aggregated for research out of all those who completed a first visit by 3/31/2014, was 787 out of 33,863 in the WTCHP (2.3%).

Outcome Assessment

Cancer incidence information is routinely collected by the WTCHP and confirmed by the NYSCR. The total number of self-reported prostate cancer cases was 442 for years 2002 through 2013; 340 of these reports were confirmed cases by the New York state cancer registries (n=208; 61%), other cancer registries (n=22; 6.5%), or medical records (n=110; 32%). Information on clinical stage, including tumor progression, nodal involvement, local and distant metastatic spread (TNM), prostate-specific antigen (PSA) concentration at diagnosis, and history of prostate hypertrophy/history of PSA testing, D'Amico score (a risk classification system, which incorporates Gleason score, clinical stage, and PSA at diagnosis and has been validated with respect to aggressiveness),[10] were collected for cases diagnosed among WTC responders. This study was approved by the Mount Sinai Program for the Protection of Human Subjects. All participants gave written informed consent.

Exposure Assessment

WTC-related environmental exposure information was obtained from questionnaires administered to cohort member at the first visit. Exposure was categorized into four mutually exclusive groups to reflect the intensity and duration of exposure to the dust, smoke, and debris.[11] Group assignment was based on the total duration of work at the WTC site, exposure to the cloud of debris from the collapse of the WTC buildings, and work on the pile of debris. [11] Among those with data on exposure, the group at very high exposure encompasses those who worked more than 90 days, were exposed to the dust cloud, and worked on the pile (N=5; 1.7%). High exposure was assigned to those who were exposed to

the dust cloud, but either worked less than 90 days or did not work on the pile (N=52; 15.3%). High and very high exposure groups were combined for analysis. Intermediate exposure comprised those who were not exposed to the dust cloud and either worked between 40 and 90 days or worked on the pile (N=174; 51.2%). Low exposure was assigned to those who worked less than 40 days, were not exposed to the dust cloud, and did not work on the pile (N=62; 18.2%). Duration of work (continuously) and location of work (on the debris pile, not on the debris pile) at the 9/11-site were also tested for associations.[1]

Statistical analysis

In the first set of analyses, age-standardized rate ratios for prostate cancer were calculated for NYSCR-confirmed WTC-respondent cases (2002-2010) compared to the New York state population (SEER*Stat),[12] using the direct standardization method, for five-year age groups and race (non-Hispanic Black, non-Hispanic White, Other), using the 2000 US reference population.[13, 14] To reduce the possibility of enrollment bias, only cases diagnosed 6 months after enrollment in the WTCHP were included. Therefore those who were diagnosed after September 11, 2001 and before enrollment in WTCHP were excluded. The number of men enrolled in the WTCHP each year served as WTC respondent denominators.

The second set of analyses focuses on characteristics of the WTC prostate cases according to exposure levels. To determine whether bias exists within the cohort based on missing clinical or exposure level data, sensitivity analyses were conducted for each missing variable separately using Pearson's chi-square (or Fisher's exact test for counts < 5). Multivariable logistic regression models adjusting for age at diagnosis (continuous) and race were then used to determine whether clinical indicators of advanced cancer were associated with either: exposure level (categorical), duration of work (continuous), or work on debris pile (dichotomous). The associations clinical indicators of advanced cancer included: Gleason scores, a histopathological diagnosis of two independent pathologists (<7 vs. ≥7); clinical stage, a surgical diagnosis for tumor extending beyond the prostate at stages III and IV vs. confined to prostate at stages I and II); and D'Amico risk score, a recurrence score based on prostate-specific antigen (PSA) before diagnosis, clinical stage, and Gleason score, (high-risk of recurrence after treatment vs. intermediate- to low- risk of recurrence). All statistical analyses were performed using Stata/SE 14.1 (StataCorp LP, College Station, TX).

RESULTS

From 2002 through 2013, 340 WTC respondents diagnosed with confirmed malignant primary prostate cancer. The mean (standard deviation) age of these responders on September 11, 2001 was 50.0 (0.4) years and 57.5 (0.4) years at prostate cancer diagnosis (range 34 to 81 years old) (**Table 1)**. Similar to the total WTC cohort, a large proportion of cases was white (58.8%), and at the time of WTCHP enrollment, had never smoked (48.8%). The highest proportions of prostate cancer cases occurred among Protective Services workers (n=116; 34.1%) and Construction workers (n=84; 24.7%) as categorized by the 2010 Standard Occupational Classification (SOC) (http://www.bls.gov/soc/home.htm), which also comprises the majority of occupations in the total WTC cohort.[11] Histologically,

most cases (n=336; 98.8%) were adenocarcinomas. Carcinomas and acinar cell carcinomas comprised one case each.

A total of 214 (63%) participants had at least one PSA screening test prior to prostate cancer diagnosis and 126 (37%) have had no PSA testing prior to diagnosis. The mean number of visits for PSA testing prior to a diagnosis of prostate cancer was 1.88 (SD ±0.10) with a range of 0 to 7 visits. At the last measurement before diagnosis, the majority of WTC participants (88.6%; n=179) had a PSA blood concentration of ≤ 9 ng/mL prior to prostate cancer diagnosis and 3 cases (1.5%) had a PSA concentration of ≥ 20 ng/mL (mean=10.4 ± 29.6 SD). A total of 83 (25.0%) of prostate cancer participants reported dysuria, including hesitancy, difficulty, and hematuria. The mean lag time between urinary symptom complaints and prostate cancer diagnosis was 0.9 years (0.01 SD). There was no correlation between the number of PSA surveillance visits and exposure level (r=0.0009) and duration of days worked on site (r=0.12).

The age-adjusted rate of prostate cancer incidence per 100,000 men between 2002-2010 for the NYS population was 261.3 (95% CI: 259.9, 262.8) and 431.6 (95% CI: 394.8, 603.7) for WTC respondents (excluding the first six months after enrolment and restricted to cases registered in the NYSCR); the standardized rate ratio was 1.65 (95% CI: 1.37, 1.93). Age-specific rate ratio estimates (**Figure 1)** were significantly higher than expected for those in age group 30-49 years (2.28; 95% CI: 1.51, 3.43), 70-74 years (2.05; 95% CI: 1.03, 4.10), and 80-84 years (5.65; 95% CI: 1.41, 22.58). When prostate cancer cases were not restricted to those diagnosed after enrollment (all NYSCR confirmed cases for 2002-2010; n=208), the standardized rate ratio was 2.20; 95% CI: 1.90, 2.50).

Among WTC cases, 74.1% (n=252) had recorded Gleason scores by WTCHP centers, with the 25.9% remainder of patients having missing scores. There was no association between missing Gleason scores or other missing characteristics and categorical exposure level (**Table 2**). Missing D'Amico and missing Gleason scores were also not associated with personal characteristics such as education, occupation, employment status, or smoking status (all p>0.05).

Missing clinical stage was associated with employment status (p=0.001); 85 cases with no clinical stage were retired (n=62), disabled (n=10), laid-off/unemployed (n=5), or working part-time (n=8). Missing clinical stage (p=0.10), Gleason scores (p=0.83), and D'Amico (p=0.22) scores were not associated with age. There was also no association between missing exposure levels and case characteristics with the exception of D'Amico risk score. For the highest D'Amico risk occurrence, 4 cases had missing exposure levels (**Table 2)**.

Among WTC respondents, 86.2% (n=293) of cases had data available on exposure levels; 57 (16.8%) had High or Very High exposures and 174 (51.1%) had Intermediate exposure. Both 3-level exposure level and working on the Ground Zero "pile" showed progressively higher ORs across clinical indicators of prostate cancer aggressiveness, although associations were statistically significant for clinical stage at the high exposure level only (**Table 3**). In stratified analyses by SOC-coded occupation, a positive relationship was found for advanced clinical stage (III or IV) among protective workers (SOC: 33-0000) (OR: 3.81; 95% CI:

0.31, 42.03) and construction workers (OR: 12.58; 95% CI: 0.74, 213.01), although this was not consistent for alternative indicators, Gleason score and D'Amico risk classification (data not shown). No association was observed between these indicators of prostate cancer aggressiveness and year of diagnosis.

DISCUSSION

Since a higher incidence of prostate cancer has been reported in WTC respondents,[1] this has been the first detailed analysis of clinical aspects of WTC-related cases as well as the first study on the association between WTC exposure and prostate cancer. Prostate cancer incidence for WTC respondents remains elevated since the 2008 analysis. For specific age groups, incidence ratios are significantly higher for those in the youngest group 30-49, 70-74, and 80-84 years. The highest WTC exposure level, which includes exposure to the dust cloud, was associated with advanced clinical stages III and IV, stages that represent tumor invasion. Other prostate cancer clinical characteristics were not statistically significant associated with exposure.

It has been recognized that prostate cancers are diagnosed more frequently in heavily screened populations compared to other populations.[15] However, we have found two key aspects to support the hypothesis of increased prostate cancer incidence rates independent of surveillance. Firstly, age-specific cancer incidence was significantly higher for WTC respondents in the youngest and two of the oldest age groups only. We would expect to find high incidence rates in across all age groups or particularly for all older age groups if an increase in surveillance was expected, particularly among men 55-69 years old when PSA testing is recommended as per the American Urological Association (AUA).[16] Secondly, the advanced clinical stage of prostate cancer cases in this cohort and lack of correlation between exposure and the number of PSA surveillance visits weighs against the argument that an observed increased incidence of prostate cancer may be a consequence of bias in PSA screening and surveillance among WTC respondents.

Both urinary symptoms and screening proportions in the WTC cohort and US populations are similar. The majority of WTC respondents had at least one PSA test and 25% of cases reported urinary symptoms prior to a diagnosis of prostate cancer, which is similar to 28.5% self-reported among US males diagnosed with prostate cancer from the National Health and Nutrition Examination Survey (2005-2006 and 2007-2008).[17]

Exposures in the 9/11 aftermath included known and suspected carcinogens. Personal protective equipment was not worn for the majority of workers and individuals in the area[19] and our study has found significant association of higher clinical stage with the highest exposure level that includes exposure to the 9/11 dust cloud. The dust cloud that resulted after the collapse of the buildings, exposed respondents to soot,[20, 21] benzene,[22] WTC dust and smoke, which contained asbestos,[23] silica,[24] cement dust,[25] glass fibers,[26] heavy metals,[27] polycyclic aromatic hydrocarbons (PAHs),[20, 28] phthalates,[29, 30] polychlorinated biphenyls,[31] and polychlorinated dibenzofurans,[32, 33] and dioxins[34] from the burning and collapse of the planes and the towers.[35] Other suspected carcinogens, such as fine particulate matter (PM2.5)[36] were elevated above that of normal levels of 2 to 6 times higher in some

areas.[37] The first of the WTC towers was 75% coated with half an inch of asbestos (up to the 40th floor), and several buildings from which dust was sampled at least three months post-9/11 contained the highest concentration of asbestos dust compared to other buildings farther away from the WTC disaster site.[38] Although a nationwide Finnish study reported an increased incidence of prostate cancer (SIR 1.21, 95% CI 1.09-1.34) among asbestos construction workers,[39] it has not yet been established whether any of these, or other, suspected carcinogens are responsible for the increase in prostate cancer observed in the WTC population. There remain few confirmed and well-established prostate cancer risk factors.[4, 40, 41] An investigation of prostate cancer tumor characteristics in relation to exposure levels among WTC respondents may generate novel biomarkers and contribute mechanistic knowledge to prostate cancer development.

WTC respondents, like many employed populations, were substantially healthier than the general population at the time of beginning their service at the WTC site, and were therefore at lower risk of cancer – at least during the first years of follow-up - than the general U.S. population, which includes persons who are chronically ill, hospitalized, or otherwise unemployable.[1, 42] Despite this healthy worker effect, our study has found a possible increase in prostate cancer incidence in comparison to the previous study conducted in 2002-2008.[11] The two largest occupational subgroups in this study included respondents in occupations that required physical and mental fitness: protective services and construction. This study is concordant with larger studies examining prostate cancer incidence among these particular occupations. Statistically significant 2.5- to- 4-fold prostate cancer risks were observed for police officers,[43] and an approximately 1.5-fold risk for firefighters.[44-46] The rate was higher particularly among men aged < 50 years in five Nordic countries[44] and a California study reported a 1.4-fold risk for firefighters aged 45-59 years.[47] A Swedish cohort study found increased prostate cancer incidence among concrete workers SIR 1.08; 95%CI 1.01 to 1.16[48] and a large study of all Nordic countries found the risk to be 1.10 (95%CI: 1.06, 1.14) among military workers.[49] Those studies did not contain analyses concerning prostate cancer aggressiveness in the respective populations. Further studies on the relationship between prostate cancer advancement and occupational or environmental exposures are needed, but have been done for other studies.

Both protective service and construction work constituted 58.8% of WTC respondent prostate cancer cases and it may be postulated that prostate cancer aggressiveness may be related to other occupation-related exposures rather than WTC-related exposures, although it is more likely that WTC-related exposures were higher in dosage. In models adjusting for both occupation and exposure level, the associations according to occupation were attenuated (OR 0.20 95% CI: 0.05, 0.85 for protective service occupations and OR 0.37 95% CI: 0.09, 1.50 for construction) while the associations were stronger when exposure was considered.

This study has a few strengths. This study also reports prostate cancer incidence in a relatively healthy, mostly non-smoking population of diverse ethnic background. It also utilizes clinical assessments of prostate cancer aggressiveness to determine the associations with exposure. This study also has limitations. Due to the small population, the range and breadth of the associations did not have enough statistical power, particularly for subgroups

of occupations. Associations for D'Amico scores and exposure may be biased due to the larger number of missing exposure levels for those with the highest score. Secondly, detailed medical information on clinical stage was missing for some cases and appears to be influenced by employment status. This may be due to a lack of outreach health programs in those who are retired or unemployed. However, a higher proportion of unemployed respondents had a higher number of visits for PSA screening. Further, sensitivity analysis revealed no difference in exposures between participants with missing and non-missing clinical characteristics. As with most solid tumors, the time period of 12 years since 9-11 may likely have been too short to capture the full effect of WTC exposure on prostate cancer risk. There was no association or pattern of decreased cancer aggressiveness with recent year of diagnosis, diminishing the possibility that these cases represent a biased sample of more aggressive cancers due to lead-time bias.

Considering the large proportion of high grade prostate cancer in younger men and the long latency for prostate cancer development continued monitoring is needed to determine alternative causes of elevated prostate cancer in the WTC population. A dose-response relationship for clinical stage, the best indicator of the local extent of tumor advancement, suggests that WTC exposure may have played a role in prostate cancer progression and possibly development. This observation warrants molecular investigations of prostate cancer in this uniquely exposed population as well as close clinical monitoring with outreach to WTC respondents by the WTCHP.

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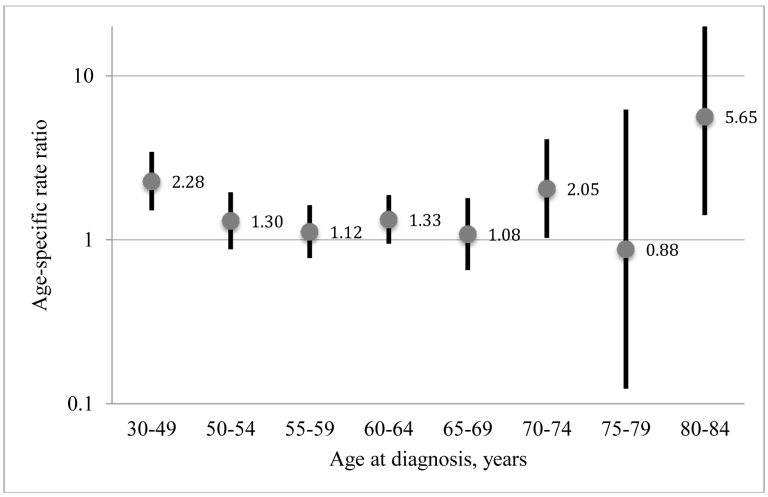

Figure 1.

Age-specific rate ratios of prostate cancer incidence per 100,000 men among WTC-respondents (n=134) compared to New York State Cancer Registry (n=81,756), 2002-2010

Table 1

Characteristics of World Trade Center Health Program prostate cancer participants, 2002 – 2013 (n=340)

Characteristic	N	%
Age on 9/11/2001, years		
30-49	155	45.6%
50-59	141	41.5%
60-69	41	12.1%
70+	3	0.9%
Age at diagnosis, years		
30-49	51	15.0%
50-59	149	43.8%
60-69	121	35.6%
70+	19	5.6%
Race/ethnicity		
Non-Hispanic white	200	58.8
Non-Hispanic black	66	19.4
Hispanic	12	3.5
Other	62	18.2
Duration of work at 9/11 site (days)		
1 – 16	85	25.0
17 – 51	73	21.5
52 – 111	59	17.4
≥ 112	77	22.6
Missing	46	13.5
Location of work		
Not on debris pile	183	53.8
On debris pile	111	32.6
Missing	46	13.5
Dust cloud exposure on 9/11		
Yes	58	17.1
No	272	80.0
Missing	10	**2.9**
Exposure level[a]		
Low	62	18.2
Intermediate	174	51.1
High or Very High	57	16.8
Missing	47	13.8
Occupation pre-9/11/2001 (NAICS code)		
Protective services (33)	116	34.1
Construction (47)	84	24.7
Transportation and Material Movers (53)	36	10.6
Electrical, Telecommunications, and O 49	26	7.7

Characteristic	N	%
Management occupations (11)	10	2.9
Building and Grounds Cleaning and (37)	8	2.4
Architecture and Mathematical	4	1.2
Occupations (17)		
Arts, design, entertainment, sport (27)	4	1.2
Retired	15	4.4
Unknown	6	1.8
Missing	7	2.1
Education		
< High School	24	7.1
High School	91	26.8
Some college	77	22.7
Associate, Undergraduate degree, or	95	27.9
Technical school		
Graduate or Professional School	38	11.2
Missing	15	4.4
Employment status		
Working	195	57.3
Disabled/Medical leave	12	3.5
Unemployed	17	5.0
Retired	74	21.2
Other	2	0.6
Missing	26	7.7

[a]Respondents were in the highest category if they were directly in the dust cloud on 9/11. They were in the very high category if, in addition to being directly in the dust cloud, they worked on the pile and worked on the site for ≥90 days. Respondents were in the intermediate or low category if they were not directly exposed to the dust cloud on 9/11. Respondents were in the low category if, in addition to not being directly exposed to the dust cloud, they also did not work on the pile and worked for < 40 days.

Table 2

Characteristics of World Trade Center Health Program prostate cancer participants aged 30-84 years

	World Trade Center respondents		Sensitivity analysis of missing data			
	New York State Cancer Registry confirmed cases (2002-2010) (n=208)	All confirmed cases[a] (2002-2013) (n=340)	Missing case characteristics and categorical exposure level		Missing categorical exposure level by case characteristics	
			χ^2	p	χ^2	p
Age at diagnosis (years), n (%)						
30-49	29 (13.9)	51 (15.0)	No missing		6.65	0.47
50-59	95 (45.7)	149 (62.1)				
60-69	72 (34.6)	121 (35.6)				
70-79	11 (5.3)	18 (5.3)				
80-84	1 (0.5)	1 (0.3)				
Race, n (%)						
Non-Hispanic white	125 (60.1)	200 (58.8)	No missing		4.76	0.09
Non-Hispanic black	46 (22.1)	66 (19.4)				
Other	37 (17.8)	74 (21.8)				
Gleason score, n (%)						
< 7	66 (31.7)	130 (38.2)	0.95	0.62	0.32	0.57
≥ 7	62 (29.8)	122 (35.9)				
Missing	80 (38.5)	88 (25.9)				
Clinical Stage, n (%)						
I	19 (9.1)	24 (7.1)	6.78	0.15	No missing	
II	90 (43.3)	102 (30.0)				
III	7 (3.4)	17 (5.0)				
IV	5 (2.4)	5 (1.5)				
Missing	87 (41.8)	192 (56.5)				
D'Amico score, n (%)						
Low	7 (3.4)	9 (2.7)	1.80	0.41	11.23	0.01
Moderate	52 (25.0)	75 (22.1)				
High	19 (9.1)	31 (9.1)				
Missing	130 (62.5)	225 (66.2)				

[a] Includes prostate cancer cases confirmed by New York State, other states, and medical records.

Table 3

Associations between exposure to 9/11 dust and prostate cancer aggressiveness among WTC responders *

	Exposure level				Duration of work days	Duration of work Per 30 days	Work on pile Yes vs. No	Dust cloud exposure
	Low	Intermediate	High	P_{trend}				
Gleason Score		N=218			N=218	N=218	N=218	N=246
<7 vs. 7+	1.0 (ref)	1.15 (0.59, 2.25)	1.22 (0.52, 2.88)	0.6	1.00 (1.00, 1.01)	1.05 (0.93, 1.17)	0.89 (0.50, 1.56)	1.06 (0.54, 2.09)
Clinical Stage		N=148			N=146	N=146	N=147	N=146
I, II vs. III, IV	1.0 (ref)	2.43 (0.51, 11.64)	5.58 (1.05, 29.76)	0.03	1.00 (0.99, 1.01)	1.01 (0.78, 1.30)	1.21 (0.27, 5.52)	2.19 (0.72, 6.69)
D'Amico risk classification		N=111			N=111	N=111	N=112	N=112
(low-to-moderate vs. high risk^)	1.0 (ref)	0.92 (0.30, 2.81)	1.54 (0.39, 6.03)	0.51	1.00 (0.99, 1.01)	0.98 (0.82, 1.16)	1.40 (0.49, 3.07)	1.54 (0.47, 4.99)

*Models adjusted for race and age at diagnosis.

^risk of post treatment recurrence