Temporal Aspects of the Association between Exposure to the World Trade Center Disaster and Risk of Cutaneous Melanoma

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Rescue/recovery workers who responded to the World Trade Center (WTC) attacks were exposed to known/ suspected carcinogens. Studies have identified a trend toward an elevated risk of cutaneous melanoma in this population; however, few found significant increases. Furthermore, temporal aspects of the association have not been investigated. A total of 44,540 non-Hispanic White workers from the WTC Combined Rescue/Recovery Cohort were studied between March 12, 2002 and December 31, 2015. Cancer data were obtained through linkages with 13 state registries. Poisson regression was used to estimate hazard ratios and 95% confidence intervals using the New York State population as the reference; change points in hazard ratios were estimated using profile likelihood. We observed 247 incident cases of melanoma. No increase in incidence was detected during 2002–2004. From 2005 to 2015, the hazard ratio was 1.34 (95% confidence interval = 1.18–1.52). A dose–response relationship was observed by arrival time at the WTC site. Risk was elevated just over 3 years after the attacks. Whereas WTC-related exposures to UVR or other agents might have contributed to this result, exposures other than those at the WTC site, enhanced medical surveillance, and lack of a control group with a similar proportion of rescue/recovery workers cannot be discounted. Our results support continued study of this population for melanoma.

INTRODUCTION

The terrorist attacks of the World Trade Center (WTC) on September 11, 2001 (9/11), in addition to their immediate lethal consequences among people present at the site and sunlight only partially explains the observed increased incidence in fair-skinned persons in the United States and other countries (Erdmann et al., 2013; Glasziou et al., 2020; Welch et al., 2021; Weyers, 2012). This trend has been attributed to increased exposure to natural (solar) and artificial UVR (Gandini et al., 2005). However, sunlight only partially explains the observed increased incidence in the United States (Welch et al., 2021). Other occupational and environmental agents are suspected to increase the risk of melanoma as well, including polycyclic aromatic hydrocarbons (Sim et al., 2020), arsenic (Matthews et al., 2019), ionizing radiation (Fink and Bates, 2005), and polychlorinated biphenyls (Boffetta et al., 2018).

A trend toward an increased risk of melanoma has been reported in previous analyses of three cohorts of WTC-exposed rescue/recovery workers (Li et al., 2012; Moir et al., 2016; Shapiro et al., 2020). Possibly because of the small number of observed events and thus limited power, the excesses did not reach statistical significance and could not be investigated in detail. In addition, the interpretation of these early results is complicated by several factors, including
differences in the definition of the exposed and the reference populations and in analytical approaches for estimating cancer risk as well as the overlap across the cohorts (Boffetta et al., 2016). In addition, there were differences in the time periods studied between WTC exposure and cancer occurrence.

To better characterize the risk of cutaneous melanoma in non-Hispanic White workers with WTC exposure, including the temporal relationship of diagnosis with exposure, we analyzed the incidence of this neoplasm in the WTC Combined Rescue/Recovery Cohort (Brackbill et al., 2021), which comprises workers enrolled in the three cohorts mentioned earlier. By examining the temporal aspects of the experience of cancer in this combined population, we aim to address the scientific question regarding the latency between environmental carcinogen exposure and the appearance of elevated incidence of melanoma among non-Hispanic White individuals.

RESULTS

Among 44,540 participants in the final analytic cohort, we observed 247 melanoma cases for 241 participants between March 12, 2002 and December 31, 2015, with 491,492 person-years of follow-up. During this period in the New York State (NYS) reference population, there were 46,233 cases of melanoma diagnosed, with 134,922,302 person-years. Demographic characteristics for the analytic cohort are presented in Table 1. A total of 9.1% of cases occurred among female responders, whereas females comprised 12.4% of responders without melanoma ($P < 0.01$); the mean age at diagnosis among melanoma cases was 55.9 (SD = 11.5) and ranged from 28 to 88. Among melanoma cases, the median time from 9/11 to diagnosis was 9.3 years (interquartile range = 6.5–12.1). Among all cases, 28 (11.6%) had another malignancy within the study period; this proportion was 6.3% among persons who were diagnosed with cancer other than melanoma in the study period ($n = 2,785$). A total of 14 of the cases of melanoma (5.8%) died during the follow-up period, compared with 3.1% of persons without melanoma ($P < 0.05$).

Tumor site and stage among the combined cohort and NYS reference data are presented in Table 2. The combined cohort had a higher proportion of localized tumors (75.7% vs. 71.4%), a lower proportion of regional tumors (5.7% vs. 9.3%; $P < 0.05$), and a similar proportion of distant tumors (4.5% vs. 4.2%) to that of NYS. Age-standardized rates were higher among WTC rescue/recovery workers for localized and regional tumors. The majority of tumors among WTC rescue/recovery workers were located on the trunk ($n = 112, 45.3%$), followed by location on the upper limb/shoulder ($n = 45, 18.2%$) and lower limb/hip ($n = 32, 13.0%$). The majority of melanomas had an unspecified histological subtype (8720, $n = 173; 70.0%$), followed by superficial spreading melanoma (8743, $n = 46; 18.6%$), nodular melanoma (8721, $n = 11; 4.5%$), and lentigo maligna melanomas (8742, $n = 6; 2.4%$). The remaining histological subtypes included regressing malignant melanoma (8723), acral lentiginous melanoma (8744), malignant melanoma in the giant pigmented nevus (8761), epithelioid cell melanoma (8771), and desmoplastic melanoma (8745), all of which had counts <5.

Figure 1 displays the adjusted incidence rates for the study. Rates were based on piecewise exponential survival models with no change points and were centered at male participants.
aged 50–59 years in the secondary models. The incidence of melanoma among the combined cohort was greater than that of NYS throughout the entire study period and increased with follow-up.

Table 3 shows the results of the analyses compared with those of the external NYS reference population. For this model, which did not evaluate change points, we observed a hazard ratio (HR) of 1.31 for melanoma (95% confidence interval [CI] = 1.15–1.48) for the whole study period (2002–2015). In our change point analysis, we estimated a change point in 2004, and the elevation in the HR was restricted to the period from 2005 to 2015 (HR = 1.34; 95% CI = 1.18–1.52). In our analysis, which only evaluated localized tumors as the outcome, we observed no change points and an increased hazard compared with those in NYS (HR = 1.36; 95% CI = 1.18–1.57). When evaluating regional/distant tumors only, model estimates were largely unstable because of the small number of tumors (results not presented).

The results of the internal analyses are reported in Table 4. In the analysis by time period of work on the WTC effort, we identified a change point in 2009, and the HR during 2010–2015 for work between 9/11 and September 17, 2001 was significantly elevated. This result contrasts with our external model mentioned earlier, which identified a change point in 2004. In the analysis examining the effect of working on the WTC pile, we identified a change point in 2004, but the results were limited by the small number of events in the period between 2002 and 2004. In the model with no change points, we observed an increased hazard among those who worked on the pile compared with that among those who did not (HR = 1.32; 95% CI = 1.00–1.74).

**DISCUSSION**

In this study, we observed an increased incidence of cutaneous melanoma among non-Hispanic White participants of the WTC Combined Rescue/Recovery Cohort compared with that among the NYS general population. Earlier assessments among participants enrolled in the Fire Department of the City of New York (FDNY), General Responder Cohort, and World Trade Center Health Registry cohorts have independently shown a trend toward an elevated risk for melanoma; however, only one showed statistical significance. Li et al. (2012) studied 21,218 rescue/recovery workers enrolled in the World Trade Center Health Registry during 2003–2004, who were followed for cancer incidence until 2008. These authors observed 18 cases of malignant melanoma through 2006 (using the population of NYS as a reference, standardized incidence ratio of 1.48; 95% CI = 0.88–2.35). In a 2016 study that extended follow-up through 2011, a significantly elevated excess incidence of cases was observed (standardized incidence ratio 1.49; 95% CI = 1.05–2.06) (Li et al., 2016). Moir et al. (2016) compared the incidence of cancer during 2001–2009 in 11,457 WTC-exposed firefighters with that in 8,220 non-WTC exposed firefighters from three urban areas of the United States. They observed 40 cases of melanoma in WTC-exposed firefighters and 21 cases in non-WTC-exposed firefighters (relative risk = 1.69; 95% CI = 0.93–3.13). Finally, Shapiro et al. (2020) investigated cancer incidence during 2002–2013 among 28,729 rescue and recovery workers who were enrolled in the General Responder Cohort using the population of the state of residence as reference. These researchers observed 50 cases of melanoma (standardized incidence ratio = 1.15; 95% CI = 0.86–1.52). Although the studies did not consistently reach statistical significance, the direction of these associations was all >1, suggesting that they were limited by few events and relatively short periods of follow-up.

This analysis corroborates these early findings and identifies a period when the risk appears to be greatest. We observed no association between WTC exposure and melanoma compared with NYS before 2005 and a 34% increased risk from 2005 until the end of the study period in 2015. However, this difference is based on a small number of cases occurring during 2002–2004 and may be due to an over-representation of FDNY cohort members in the early period.
with the duration of residence in these areas. In addition, the risk of melanoma seems to be lower in the absence of significant sun exposure during childhood (Autier and Doré, 1998). These results reinforce the notion that heavy exposure to the sun during childhood would be a major factor determining the occurrence of melanoma in adult life. In this respect, the increased risk observed beginning from 3 years after the attacks in the present analysis may reflect numerous factors other than the latency solely attributable to WTC-related exposures. It is plausible that the carcinogenicity of exposures other than UVR experienced on the WTC effort may have contributed to the observed associations. Other phenomena such as environmental and occupational exposures that occurred outside the WTC experience must also be considered. Another plausible explanation aside from a short induction period is a detection bias owing to oversurveillance in this cohort, which we were not able to investigate in this study. The synergy between WTC exposures, sun exposure, augmented surveillance, and cumulative occupational exposures may have all contributed to the observed early onset of disease.

The WTC Combined Rescue/Recovery Cohort includes firefighters, law enforcement, and construction workers. An increased risk of melanoma has consistently been reported in previous studies of firefighters (Casjens et al., 2020) and police officers (Finkelstein, 1998; Forastiere et al., 1994; Harris et al., 2018), whereas the results of studies of construction workers are mainly negative (Alicandro et al., 2020; Gallagher et al., 1987; Håkansson et al., 2001; Robinson et al., 1995). Workplace exposure to UVR has been suggested to explain these findings because other exposed occupational groups, such as offshore workers (Stenehjem et al., 2017), airline pilots and cabin crews (Sanlorenzo et al., 2015), and agricultural workers (Kachuri et al., 2019), also experience an increased incidence of melanoma. However, the excess in melanoma risk is mainly observed among subjects with intermittent, prolonged UV exposure (Autier and Doré, 2020). These findings do not support the hypothesis of a causal role of WTC-related UVR exposure that, on average, was of relatively short duration (i.e., <1—9 months). We cannot exclude a role of UV exposure experienced by cohort members outside of WTC-related operations. The role of other agents that were present at the WTC site, such as polycyclic aromatic hydrocarbons and polychlorinated biphenyls (Liory and Georgopoulos, 2006), is also plausible, although an estimate of their contribution is complicated by the lack of exposure data.

Increased medical surveillance is an alternative explanation of our findings. An increase in the incidence of melanoma, in particular the more superficial forms of the disease after enhanced surveillance, has been described in several populations (Armstrong and Kricker, 1994; Bagley et al., 1981; Glassiú et al., 2020; Welch et al., 2021; Weyers, 2012) and is supported by the increased rate of early-stage melanomas among rescue/recovery workers. The WTC Health Program does not cover skin examinations, and although plausible, it is unlikely that melanoma is discovered.
as part of routine medical monitoring examinations. We found a 36% increased risk over the entire study period in our analysis, which was restricted to localized tumors only, suggesting that surveillance bias is not entirely responsible for the observed association. An earlier study investigating cancer among WTC-exposed firefighters workers more broadly found that responders who had surveillance chest computed tomography scans through the WTC Health Program ≤6 months before a cancer diagnosis (lung, liver, thyroid, non-Hodgkin lymphoma, and kidney) may have been at increased probability for early detection (Shapiro et al., 2020; Zeig-Owens et al., 2011). Similarly, prostate cancer and hematologic neoplasms diagnosed within 6 months of routine blood tests performed within the program may also be subject to surveillance bias.

The main strength of our study is that there was greater statistical power than previous analyses of WTC rescue and recovery workers, leading to a detailed assessment of temporal aspects of the association and the ability to conduct internal dose–response analyses. In addition, by including 13 different states in the linkages of the cohort to central cancer registries, we were able to cover 93% of the addresses of the 44,540 member study population. Earlier works reported the suggestion of an elevated risk among WTC-exposed participants, and in this study, a significantly elevated risk, which to our knowledge was previously unreported, of over 30% for 247 cases of melanoma was observed. In our internal analysis, after adjusting for individual WTC cohort (which may be an important proxy for access to insurance and cancer coverage), the association was attenuated but still significant.

Limitations include the lack of quantitative data of exposure to carcinogens in WTC rescue/recovery operations as well as the lack of information on the potential confounding effects of occupational and recreational exposures to UV and other agents outside the WTC experience. Moir et al. (2016) did not find a significantly elevated risk of cutaneous melanoma among WTC-exposed firefighters relative to that in a pooled cohort of non-WTC exposed firefighters from the San Francisco, Chicago, and Philadelphia departments, and an overview paper by Laroche and L’Espérance (2021) noted an overall increased risk of malignant melanoma for firefighters compared with that for the general population. Although we note that firefighters represent <30% of the overall WTC-exposed rescue/recovery cohort. Nonetheless, a non-WTC-exposed occupational comparison cohort with similar professions represented rather than the general NYS population may have offered an advantage for this study. We also did not have data on clinical characteristics such as Breslow depth and Clark level or frequency of skin examinations, but detailed skin examinations are not part of the WTC annual medical examination. Another weakness was that we did not have adequate power to study melanoma in non-White races. Other authors have found that among non-White racial groups, particularly African Americans, the incidence of cutaneous melanoma is lower overall, yet with a higher proportion of advanced-stage tumors (Cormier et al., 2006; Cress and Holly, 1997; Wang et al., 2016). In addition, we observed a preponderance of truncal melanomas among both WTC rescue/recovery patients and NYS patients in general. However, melanoma incidence was elevated for nearly all body parts compared with NYS age-adjusted rates. It was observed that after controlling for stage, relative mortality is similar (Mahendraraj et al., 2017; Ward-Peterson et al., 2016), and the high incidence of advanced-stage tumors may reflect poorer access to preventative care. Thus, further investigation of the role of latency in cutaneous melanoma is needed in more ethnically diverse cohorts.

Table 4. Hazard Ratio of Cutaneous Melanoma by Period of Work at WTC Site. Results of Internal Comparison

| N Change Points | Period of Follow-Up | First Worked at WTC Site | N Cases | Person-Years | HR    | 95% CI |
|-----------------|---------------------|--------------------------|---------|--------------|-------|--------|
| 0               | 2002–2015           | Early                    | 191     | 386,865      | 1.28  | 0.89–1.85 |
|                 |                     | Late                     | 40      | 82,820       | Ref   |        |
| 1               | 2002–2009           | Early                    | 66      | 186,643      | 0.68  | 0.42–1.09 |
|                 |                     | Late                     | 26      | 38,536       | Ref   |        |
|                 | 2010–2015           | Early                    | 125     | 200,222      | 2.41  | 1.36–4.27 |
|                 |                     | Late                     | 14      | 44,285       | Ref   |        |

Adjusted for age, sex, calendar year, and cohort membership

| N Change Points | Period of Follow-Up | First Worked at WTC Site | N Cases | Person-Years | HR    | 95% CI |
|-----------------|---------------------|--------------------------|---------|--------------|-------|--------|
| 0               | 2002–2015           | Early                    | 191     | 386,865      | 1.03  | 0.69–1.52 |
|                 |                     | Late                     | 40      | 82,820       | ref   |        |
| 1               | 2002–2009           | Early                    | 66      | 186,643      | 0.54  | 0.32–0.88 |
|                 |                     | Late                     | 26      | 38,536       | ref   |        |
|                 | 2010–2015           | Early                    | 125     | 200,222      | 1.93  | 1.07–3.48 |
|                 |                     | Late                     | 14      | 44,285       | ref   |        |

Abbreviations: CI, confidence interval; HR, hazard ratio; WTC, World Trade Center.

The 0 change point model estimates the hazard over the course of the study period, 2002–2015; and the 1 change point model is independent and estimates the hazard in two distinct intervals, from 2002 to 2009 and from 2010 to 2015.

Early = first self-reported working at the main WTC disaster site between 11 September 2001 to 17 September 2001; Late = first self-reported working at the WTC disaster site between 18 September 2001 to 30 June 2002. Melanoma cases among persons who did not self-report working at the main WTC site between 11 September 2001 to 30 June 2002 were excluded from this analysis (n = 16 persons; 16 cancer cases).
In conclusion, our analysis confirmed an increased incidence of melanoma among non-Hispanic White WTC rescue/recovery workers. Compared with that among the NYS population, the increase in incidence started after 2004 and persisted despite the extension of the follow-up. This result and the result from internal analyses showing a higher risk for those who responded shortly after the attacks are consistent with a contributory role of WTC exposure, but alternative explanations cannot be excluded. Regardless of the precise causes, the results support the continued study of this population for melanoma.

MATERIALS AND METHODS

Study population

The study population included all eligible rescue/recovery workers from three WTC-exposed responder cohorts: the FDNY (Webber et al., 2011), the General Responder Cohort (Herbert et al., 2006), and the World Trade Center Health Registry (Farfel et al., 2008). Rescue/recovery workers included firefighters, emergency medical service providers, law enforcement, construction and communication workers, volunteers, and cleanup workers. All adult rescue/recovery workers who were members of any of the three cohorts and provided written informed consent for the research or who fell under a waiver of consent approved by the Institutional Review Board of the cohort institution were eligible for inclusion in the study. Additional details regarding the consolidation of the WTC Combined Rescue/Recovery Cohort (referred to as combined cohort in the remaining part of this paper), including deduplication of subjects and data harmonization, are described elsewhere (Brackbill et al., 2021).

A total of 24,562 members of the combined cohort were excluded from the analysis for the following reasons: (i) aged <18 years on 9/11 (n = 165); (ii) missing date of birth (n = 21); (iii) enrolled in the cohort after October 1, 2012 (n = 4,402); and (iv) belonging to race and ethnicity other than non-Hispanic White (n = 19,974). Only 7 (0.04%) of the 19,974 participants with race/ethnicity other than non-Hispanic White had melanoma. This analysis is therefore based on 44,540 non-Hispanic White rescue/recovery workers enrolled in the cohort before October 1, 2012 (i.e., when cancer coverage began under the James Zadroga 9/11 Health and Compensation Act) (Centers for Disease Control and Prevention, 2020) and were aged at least 18 years on 9/11.

Outcome assessment

Person-time accruals began on the later of March 12, 2002 or 6 months after the date of enrollment into a WTC rescue/recovery cohort. The date of March 12, 2002 was chosen so that prevalent cancers already developed before 9/11 were not misclassified as incident cases; 6 months was chosen to reduce selection in the cohorts after the onset of symptoms. The follow-up period ended at death or on December 31, 2015. Incident cases of melanoma defined (using the surveillance, epidemiology, and end result site recode table [25010]) as International Classification of Diseases for Oncology, third edition topography code C44 and malignant behavior code 3 were obtained by matching the combined cohort to data from the cancer registries of the following states: Arizona, California, Connecticut, Florida, Massachusetts, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Texas, Virginia, and Washington. The 13 states accounted for 93.1% of the known addresses of the 99.5% of persons with known addresses who were included in the study. We were missing the state of residence for 113 of the 44,540 persons included in the analysis. Tumor characteristics, such as diagnosis date, histology, and stage, were provided by state cancer registries. Cases of cancers obtained from multiple registries for the same participant were identified, and duplicates were excluded. For the calculations of age at diagnosis and person-time at risk, the 15th of each month was used. For the few participants who were missing a birth month, June was used. Death dates available for each cohort were reconciled by the NYS cancer registry to ensure precise mortality ascertainment and person-time contributions.

Exposure measures and demographic characteristics

The specific measures used for this study included dust exposure on 9/11 and work periods on the WTC effort (Weakley et al., 2011). The exposure measure for our primary external analysis was presence at the WTC site or WTC rescue/recovery work at other sites such as the Fresh Kills Landfill at any time from 9/11 to June 30, 2002, the time when the WTC Manhattan site closed. We used two additional exposure variables: (i) work on the WTC pile (yes or no); (ii) time of the first arrival at the WTC disaster sites (9/11 to September 17, 2001 or September 18, 2001 to June 30, 2002). Basic demographic characteristics such as sex, birth month, birth year, and race/ethnicity were used for data analysis.

NYS comparison population

Incident melanoma tumors in NYS were selected as the reference for our external analysis and were obtained and organized using SEER*stat software (National Cancer Institute, Bethesda, MD) (National Cancer Institute, 2020). Data were summarized in strata of persons and cases by age (in 5-year increments), sex, and calendar year (2002–2015).

Statistical analyses

We first calculated age-standardized incidence rates by primary site and stage for the combined cohort and the NYS comparison population. Rates were standardized to the United States 2000 male and female populations, and NYS rates, such as the WTC combined cohort, were restricted to non-Hispanic White participants. The outcome for all multivariable analyses was incident melanoma. Both comparison rates and observed cancer counts included multiple primary cancers for each person. That is, persons with melanoma were counted as a case even if they had cancer before the start of follow-up for this study (i.e., the later of March 12, 2002 or 6 months after enrollment). Persons could be counted more than once if they were diagnosed with >1 melanoma. The combined cohort data were grouped in strata of person-time and cases in the same way as the NYS comparison population.

We used piecewise exponential survival models to estimate the HRs and associated 95% CIs. This approach is similar to Cox regression but allows baseline hazard to change at numerous time intervals rather than with every event; 1-year time intervals were used (Jensen and Lütkemohrt, 2008). This model also allowed for incidence to be estimated in the reference group so that the HRs have rate ratio (relative rate) interpretations. The HRs could vary through the follow-up period using change points to model the time at which the HRs varied. The model is mathematically identical to a Poisson model where the rates in the reference population vary each year, and the rate ratios/HRs are allowed to vary one or more times over the follow-up period. The data are used to estimate the time...
where the change(s) in HRs are most significant, and in fact, we fit the model as a Poisson model. The specific model is as follows: Let \( Y_{ik} \) be the number of incident cases of melanoma, modeled to follow a Poisson distribution given the covariates; \( T_{ik} \) is the total person-time at risk, for each particular stratum \( i \) and time interval \( k \); \( a_{ik} \) is the time since exposure; and exposures are indicated by the values of \( x_{ik} \), a binary variable taking the value of 1 for the WTC-exposed cohort and 0 for the comparison NYS population. The \( w_{ik} \)'s are dummy variables representing the 1-year time intervals; the \( a_{ik} \)'s are parameters representing the baseline hazard as a function of time that has a cases-per-person-time interpretation. \( \beta_j \) is the log HR, which is also a log rate ratio as mentioned earlier, which compares incidence in the WTC-exposed cohort with that in the NYS reference population for time interval \( j \) (\( j \geq 1 \)), which is the period between change points \( \tau_{j-1} \) and \( \tau_j \). \( z_{ij} \) represents sex, calendar year, and age. Equation 1 is found below and is described in greater detail elsewhere (Jensen and Lütkebohmert, 2008). This primary external analysis using NYS as a comparison controlled for age and calendar year.

\[
\begin{align*}
\text{Equation 1: } \log(Y_{ik}) &= \log(T_{ik}) + \sum_{k=1}^{12} a_{ik} w_{ik} + \\
&+ \sum_{j=1}^{p+1} \beta_j X_{ij} (\tau_{j-1} < t_{ik} \leq \tau_j) + \sum_{j=1}^{p} \gamma_j z_{ij}.
\end{align*}
\]

The change points are estimated using profile likelihood (Glaser et al., 2014; Goodman et al., 2011; Hall et al., 2003, 2001, 2000). In practice, this consisted of fitting a series of models for different candidate change points in which each year’s number of cases, offset by person time, was combined with other years before the candidate change point, and the number of cases after the candidate change point, offset by person time, were similarly combined. The relative hazard after/before each candidate change point was estimated, the likelihood for each candidate change point was compared, and the change point with the best fit based on the likelihood was selected. Thus, 12 possible models with a change point at each year between 2003 and 2014 were evaluated. This has significant advantages over simply presenting each year’s absolute and relative hazard because there is greater power to identify a time at which the relative hazard changes. Four additional analyses were conducted. The first was an external analysis that evaluated localized tumors, separately, to address the potential for surveillance bias. The second was an internal analysis that evaluated two distinct periods of time during which participants first worked on the WTC effort (9/11 to September 17, 2001; September 18, 2001 to June 30, 2002; referred to as early and late, respectively, in the remaining part of this paper); these mutually exclusive categories were included as binary variables. The third was an internal analysis that evaluated participants who worked on the WTC pile versus those who did not. Finally, the fourth model controlled for WTC cohort membership (i.e., FDNY, General Responder Cohort, and World Trade Center Health Registry) as well as for the other covariates used in the second analysis. We controlled for cohort membership to account for an uneven distribution of period in which participants first worked at the WTC site (e.g., FDNY had the highest proportion of participants who first worked at the WTC site in the early period). For each analysis, change points were separately evaluated.

The same model equation was applied to internal models as to the external model, except that the WTC variable was replaced with time first worked on the WTC effort. We also calculated the adjusted baseline incidence rates stratified by exposure category. For this analysis, we applied a Locally Weighted Scatterplot Smoothing function for point estimates (Hastie and Tibshirani, 1986).

Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (von Elm et al., 2007) and was approved by Institutional Review Boards at Albert Einstein College of Medicine (Bronx, NY), New York City Department of Health and Mental Hygiene (Long Island City, NY), the New York State Department of Health, and all the 13 cancer registries. The Icahn School of Medicine at Mount Sinai Institutional Review Board ruled the research exempt.

**Data availability statement**

Data that support the findings of the study may be obtained from the corresponding author (PB) upon reasonable request after approval by the Steering Committee for “Incidence, Latency, and Survival of Cancer Following World Trade Center Exposure” (National Institute for Occupational Safety and Health Cooperative Agreement U01 OH011932) in accordance with the study’s official Data Sharing Plan.

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**AUTHOR CONTRIBUTIONS**

Conceptualization: PB, DGG, RZO, JEC, MJS, CBH; Funding Acquisition: PB, CBH; Methodology: PB, DGG, RZO, CBH; Writing – Original Draft Preparation: PB, DGG, RZO, CBH; Writing – Reviewing and Editing: PB, DGG, RZO, DK, JL, RMB, MRF, JY, ARK, BQ, MJS, MPW, DJP, CRD, ACT, CBH

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are solely the responsibility of the authors and do not necessarily represent the official views of the CDC National Institute for Occupational Safety and Health.

ACKNOWLEDGMENTS

We thank the 13 state cancer registries for carrying out record linkages: Bureau of Cancer Epidemiology, New York State Department of Health (DOH); Arizona Cancer Registry Department of Health Services; California Cancer Registry, Department of Public Health; Connecticut Tumor Registry, Connecticut Department of Public Health; Florida Cancer Registry, Florida DOH; Massachusetts Cancer Registry, Massachusetts Department of Public Health; New Jersey State Cancer Registry; New Jersey DOH and Rutgers Cancer Institute of New Jersey; North Carolina Central Cancer Registry, State Center for Health Statistics; Ohio Cancer Incidence Surveillance System, Ohio DOH; Bureau of Health Statistics and Research, Pennsylvania DOH; Texas Cancer Registry, Texas Department of State Health Services; Virginia Cancer Registry, Virginia DOH; and Washington State Cancer Registry, Washington DOH. The collection of cancer incidence data used in this study was supported by the California Department of Public Health according to California Health and Safety Code, Section 103685; Centers for Disease Control and Prevention (CDC)'s National Program of Cancer Registries, under cooperative agreement NUS5DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN2612018000321 awarded to the University of California, San Francisco; contract HHSN2612018000315 awarded to the University of Southern California; and contract HHSN261201800009I awarded to the Public Health Institute. The Connecticut Department of Public Health Human Investigations Committee approved this research project, which used data obtained from the Connecticut Department of Public Health. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System, the statewide cancer registry funded by the Florida DOH and the CDC National Program of Cancer Registries. Cancer incidence data used in these analyses were obtained from the Ohio Cancer Incidence Surveillance System, Ohio DOH, a cancer registry partially supported by the National Program of Cancer Registries at the CDC through Cooperative Agreement Number NU58DP006284. These data were supplied by the Bureau of Health Statistics and Registries, Pennsylvania DOH (Harrisburg, PA). Additional contributions were as follows: Molly Skerker provided substantial administrative support in the initial phase of this study. This research was supported through the National Institute for Occupational Safety and Health and cooperative agreements (U10OH011315, U01OH011932, U01OH011681, U01OH011931, U01OH011480, and U01OH009739) and contracts (200-2011-39378, 200-2017-93325, and 200-2017-93326). In addition, this research was supported by cooperative agreement 6U58DP006309 awarded to the New York State DOH by the CDC and by contract 75N9101DB00005 (Task Order 75N9101DB00011) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services (Bethesda, MD). This research was also supported by cooperative agreement U50ATU272750 from the Agency for Toxic Substances and Disease Registry, CDC, which included support from the National Center for Environmental Health, CDC and by the New York City Department of Health and Mental Hygiene. This research was also supported by grant P30 CA103330 from the National Cancer Institute, National Institutes of Health. All authors received grant and/or contract support from the National Institute for Occupational Safety and Health. In addition, CBH is supported by the National Institute of Aging and the National Cancer Institute.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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