MEASUREMENT AND EVALUATION OF RISK FACTORS FOR

CANCERS OF THE HEAD AND NECK IN A COHORT OF

9/11 WORLD TRADE CENTER RESPONDERS

By

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A dissertation submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Graduate Program in Public Health

Written under the direction of

Judith M. Graber, PhD, MS

And approved by

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New Brunswick, New Jersey

May 2019

ABSTRACT OF THE DISSERTATION

Measurement and Evaluation of Risk Factors for Cancers of the Head and Neck in a Cohort of 9/11 World Trade Center Responders

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Background: Responders to the World Trade Center (WTC) on 9/11 and throughout the subsequent rescue, recovery, and cleanup efforts were potentially exposed to a host of known and suspected human carcinogens. Emerging research suggests that head and neck cancers (HNCs) may be among the health consequences of involvement in the World Trade Center (WTC) response efforts that followed September 11, 2001.

Objective and Specific Aims: This dissertation sought to identify risk factors for HNC among WTC Health Program general responders. Three specific aims supported this goal: (1) develop and assess the reliability of a questionnaire designed to retrospectively reconstruct risk behaviors before, during, and after the WTC exposure period; (2) evaluate WTC-related and behavioral risk factors for HNC among WTC responders using a nested case-control approach; and (3) compare the distribution of risk factors for HNC subsites among WTC responders using a case-case approach.

Methods: A questionnaire was developed to retrospectively assess risk behaviors for HNC, including tobacco use, alcohol consumption, and sexual activity and administered to 64 cases (responders with HNC) and 136 controls identified via risk-set sampling and matched on age, sex, and race/ethnicity. For study 1, Cohen's kappa and intraclass correlation coefficient were used to assess agreement of the questionnaire's measures of tobacco and alcohol use with data previously collected during WTCHP monitoring visits using. For study 2, WTC exposures and behavioral risk factors were compared between cases and controls using conditional logistic regression models. For study 3, risk factor profiles were compared among cases with oropharyngeal, oral cavity, laryngeal, and other HNCs using bivariate statistics (ANOVA, Chi-Square, Fisher's Exact) and unconditional logistic regression.

Results: Study 1 found high agreement between most measures common to both data sources but noted some differences in agreement by disease status and survey mode. The nested case-control analysis (Study 2) found estimated HNC risk associated with having a protective services occupation, lifetime and post-WTC cigarette smoking, and post-WTC number of sex partners. Increased risk was also associated with arriving on 9/11 as opposed to later, but only among responders without protective services occupations. The case-case analysis (Study 3) revealed differential risk factor profiles by cancer site that did not fully align with what is seen in the general population.

Conclusion: The findings from this dissertation contribute to development of a unique HNC risk factor profile and inform potential HNC risk mitigation strategies for WTC responders. These recommendations may assist WTCHP clinicians with identifying high-risk responders and thus improve HNC detection and treatment outcomes in this population.

ACKNOWLEDGEMENT

I would like to thank my dissertation committee, Dr. Judith Graber, Dr. Marian Passannante, Dr. Pamela Ohman Strickland, and Dr. Anna Giuliano, for their guidance throughout this process. I especially want to thank Dr. Graber for her unwavering support these past few years and for pushing me to be better than I believed I could be.

I also want to thank the WTC-CARES study team for their invaluable contributions to this work, as well as the WTC-CARES interviewers, and the WTCHP General Responder Data Center. I also would also like to recognize the WTC responders, for their sacrifices during the WTC response efforts.

I would like to thank the faculty, staff, and students at Rutgers School of Public Health and my colleagues at the Center for Tobacco Studies. Their support has been instrumental in my academic, professional, and personal successes.

Finally, I would like to acknowledge my friends and family. I especially thank my parents, W. James and Carla Bover, for their unconditional love and guidance throughout this and countless other challenges. I would also like to thank my siblings, Raymond, Kristen, and Michael, for always cheering me on, even from many miles away. Last but certainly not least, I thank my husband, Gregory Manderski – this accomplishment would not have been possible without his unwavering encouragement, reassurance, and devotion.

I dedicate this dissertation to my children and continuous sources of inspiration, Owen and Vanessa Manderski.

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INTRODUCTION

The collapse of the World Trade Center (WTC) buildings on September 11, 2001 (9/11) resulted in unprecedented toxic pollution that persisted for several months, potentially exposing more than 400,000 people, including those involved in the WTC response efforts, to multiple known and suspected human carcinogens, including asbestos, silica, benzene, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, volatile organic compounds, and a variety of dusts and metals.[1-4] Given that the primary route of exposure to these substances was inhalation by mouth,[5] cancers of the head, neck, and upper respiratory tract are plausible health consequences of exposure to the dust and debris during the WTC response efforts.

Epidemiology of Head and Neck Cancers

Head and neck cancers (HNC) include malignancies of the oral cavity, pharynx, larynx, nasal cavity, paranasal sinus, and salivary glands and comprise approximately 3% of cancers diagnosed in the United States.[6] HNC incidence is notably higher among men than women, with rate ratios ranging from 2.7 (95% CI: 2.7, 2.8) for oral cavity and pharyngeal cancer to 4.5 (95% CI: 4.4, 4.6) for laryngeal cancer.[6] Risk for these cancers increases with age and the median age at diagnosis in the United States is 63 years;[7] however, certain subtypes of HNC, particularly oropharyngeal cancers attributed to human papillomavirus (HPV) infection, tend to occur in younger age groups.[8] HNC mortality varies by site and stage and is a function of survival and staging at diagnosis.[9] For example, 5-year relative survival for oral and pharyngeal cancers diagnosed at the local stage is high, 83%. However, in the absence of effective screening, locally staged diagnoses account for just 30% of these cancers.

Tobacco smoking is a well-established risk factor for HNC. Multiple studies have found strong dose-response effects, such that relative odds of HNC increases with frequency, duration, and pack-years (a cumulative smoking measure defined as years of smoking × packs per day) of smoking.[10-15] Low frequency cigarette smoking is also associated with greater odds of HNC, and this effect strengthens with increasing duration of smoking.[16,17] In addition, cigar and pipe smoking are positively associated with HNC, independent of cigarette smoking.[18-22] Heavy alcohol consumption is also causally associated with HNC,[10,12,23,24] with a synergistic effect in the presence of tobacco smoking.[25-28] Other suggested behavioral risk factors for HNC include use of certain types of smokeless tobacco use and marijuana smoking, however findings from research on these topics are inconsistent.[13,29-32]

Persistent oral infection with oncogenic HPV, particularly type 16,[33,34] is associated with a subset of HNCs that are epidemiologically and etiologically distinct. In contrast to “traditional” HNCs, rates of HPV-positive oropharyngeal cancer diagnoses are increasing, likely driven by increases in incidence of HPV infection,[35,36] and tend to occur among middle-aged adults without significant history of smoking and drinking.[37-40] These cancers are instead associated with sexual behavior, including number of oral and vaginal sex partners and age at sexual debut, tooth loss, and tonsillectomy.[28,38,41-44] Survival rates for HPV-associated HNCs are generally better than those not associated with HPV,[45] and HPV-seropositive status is a well-documented positive prognostic indicator,[45-52] further distinguishing HPV-positive from other HNC tumors.

Several environmental and occupational agents are associated with HNC.[53] Numerous studies have linked occupational asbestos exposure to cancers of the larynx and pharynx,[54-57] and one study of laryngeal cancer observed a synergistic joint effect between asbestos exposure and tobacco smoking.[58] In addition, wood dust, leather, and cement dusts are associated with certain HNCs including cancers of the nasal cavity, paranasal sinus, nasopharynx, pharynx, and larynx.[27,59-61]

World Trade Center Exposure

The attacks on 9/11 and subsequent collapse of the WTC towers introduced a complex mix of air pollutants, and it is estimated that more than 400,000 people, including those involved in the rescue, recovery, and cleanup efforts (WTC responders), were exposed to multiple potential toxicants.[1-4] These included substances that are strongly associated with HNC, such as asbestos and wood, leather, and cement dusts.[27,53-61] In addition to the initial dust, smoke, vapors, and fumes, exposure potential continued for several months due to resuspension of the dusts into the air as cleanup continued on the pile and at the landfill on Staten Island.[3] The presence of HNC agents in the air, coupled with the primary route of exposure being inhalation by mouth and high intensity of exposure in the initial days of WTC response efforts,[62] make HNCs a plausible health consequence of WTC exposure.

In response to concerns about the health effects of these exposures, the WTC Medical Monitoring and Treatment Program (MMTP) launched to provide medical monitoring and treatment to WTC responders. In 2011, enactment of the James Zadroga 9/11 Health and Compensation Act of 2010 created the WTC Health Program (WTCHP), consolidating the MMTP and other programs, to continue providing medical monitoring and treatment for WTC-associated conditions to WTC responders.[63] The WTCHP General Responder Cohort (GRC) is a voluntary open cohort of eligible responders (other than New York City Fire Department [FDNY] responders, who are followed separately) who worked or volunteered between 9/11 and July 31, 2002.[63] An estimated 90,000 responders may be eligible for GRC membership;[1] as of December 2016, about 40,000 were enrolled in the cohort.[64] WTCHP GRC members receive an initial physical examination and undergo annual health monitoring visits thereafter. The WTCHP General Responder Data Center in the Icahn School of Medicine at Mount Sinai in New York City maintains data collected from consenting GRC members during enrollment and follow-up. This includes clinical, questionnaire, and WTC exposure information, which can be available for research purposes.

Studies of WTC-exposed populations followed through 2008 have reported modest excesses of all and other specific cancer sites, including prostate and thyroid, among WTC-exposed populations.[65-67] In response to WTCHP clinician concerns about elevated numbers of HNC cases among GRC members,[68] a subsequent analysis of cancers diagnosed between 2009 and 2012 among WTCHP GRC member found a 40% excess (standardized incidence ratio [SIR], 1.4 [95% CI, 1.01-1.89]) of HNC.[69] This finding may be subject to surveillance bias, given that the excess was observed among a self-selected and highly monitored cohort, or healthy worker effect.[70] In addition, the study could not explore the impact of other important risk factors, such as alcohol consumption and sexual behavior.

The observed excess of HNC among GRC members may be attributable to WTC exposure, but GRC members may also be at increased risk for HNC due to lifetime risk factors unrelated to WTC exposure, such as tobacco use, heavy alcohol consumption, or HPV infection. In addition, these risk behaviors may have changed during or after the WTC response (e.g., increased alcohol consumption, relapse to smoking), and interaction among risk factors is possible. Therefore, the possible effects of WTC exposures on HNC risk may be direct, mediated, or moderated, warranting careful consideration of WTC exposures in the context of other risk factors before, during, and after the WTC response. Retrospective assessment of these behaviors is therefore critical for assessing the role of WTC exposure and other risk factors in HNC etiology among WTC general responders.

Research Objectives

There is no effect screening for HNC, however development of a risk factor profile for WTC responders may assist WTCHP clinicians with identifying high-risk responders, which may in turn improve detection and treatment outcomes in this population. As such this research seeks to elucidate the role of World Trade Center exposure in head and neck cancer incidence in the context of behavioral risk factors. Three specific aims support this goal: (1) develop and assess the reliability of a questionnaire designed to retrospectively reconstruct risk behaviors before, during, and after the WTC exposure period; (2) evaluate WTC-related and behavioral risk factors for HNC among WTC responders using a nested case-control approach; and (3) compare the distribution of risk factors for HNC subtypes among WTC responders using a case-case approach.

REFERENCES

1. Murphy J, Brackbill RM, Thalji L, Dolan M, Pulliam P, Walker DJ. Measuring and maximizing coverage in the World Trade Center Health Registry. *Stat Med.* 2007;26(8):1688-1701.
2. Landrigan PJ, Lioy PJ, Thurston G, et al. Health and environmental consequences of the world trade center disaster. *Environ Health Perspect.* 2004;112(6):731-739.
3. Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives.* 2002;110(7):703-714.
4. Pleil JD, Vette AF, Johnson BA, Rappaport SM. Air levels of carcinogenic polycyclic aromatic hydrocarbons after the World Trade Center disaster. *Proc Natl Acad Sci U S A.* 2004;101(32):11685-11688.
5. Cohen MD, Vaughan JM, Garrett B, et al. Acute high-level exposure to WTC particles alters expression of genes associated with oxidative stress and immune function in the lung. *J Immunotoxicol.* 2015;12(2):140-153.
6. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
7. Noone AM HN, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015. 2018; https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Accessed March 15, 2019.
8. Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). *Oral Oncol.* 2015;51(8):727-730.
9. ACS (American Cancer Society). *Cancer Facts & Figures 2017.* Atlanta, GA: American Cancer Society; 2017.
10. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res.* 1990;50(20):6502-6507.
11. Ahrens W, Jockel KH, Patzak W, Elsner G. Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. *Am J Ind Med.* 1991;20(4):477-493.
12. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48(11):3282-3287.
13. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF. Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. *Cancer Causes Control.* 2013;24(4):649-664.
14. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst.* 2007;99(10):777-789.

15. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort. *Head Neck.* 2013;35(7):914-922.
16. Berthiller J, Straif K, Agudo A, et al. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-845.
17. Lubin JH, Purdue M, Kelsey K, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol.* 2009;170(8):937-947.
18. Fernandez Garrote L, Herrero R, Ortiz Reyes RM, et al. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. *British Journal of Cancer.* 2001;85(1):46-54.
19. Wyss A, Hashibe M, Chuang SC, et al. Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Am J Epidemiol.* 2013;178(5):679-690.
20. Iribarren C, Tekawa IS, Sidney S, Friedman GD. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med.* 1999;340(23):1773-1780.
21. Carstensen JM, Pershagen G, Eklund G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25 000 Swedish men. *Journal of Epidemiology and Community Health.* 1987;41:166-172.
22. Randi G, Scotti L, Bosetti C, et al. Pipe smoking and cancers of the upper digestive tract. *Int J Cancer.* 2007;121(9):2049-2051.
23. Elwood JM, Pearson JC, Skippen DH, Jackson SM. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Cancer.* 1984;34(5):603-612.
24. Freedman ND, Schatzkin A, Leitzmann MF, Hollenbeck AR, Abnet CC. Alcohol and head and neck cancer risk in a prospective study. *Br J Cancer.* 2007;96(9):1469-1474.
25. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev.* 2009;18(2):541-550.
26. Maasland DH, van den Brandt PA, Kremer B, Goldbohm RA, Schouten LJ. Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. *BMC Cancer.* 2014;14:187.
27. Vlajinac HD, Marinkovic JM, Sipetic SB, Andrejic DM, Adanja BJ, Stosic-Divjak SL. Case-control study of oropharyngeal cancer. *Cancer Detect Prev.* 2006;30(2):152-157.
28. Lissowska J, Pilarska A, Pilarski P, et al. Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev.* 2003;12(1):25-33.
29. Wyss AB, Hashibe M, Lee YA, et al. Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium. *Am J Epidemiol.* 2016.

30. Accortt NA, Waterbor JW, Beall C, Howard G. Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control.* 2005;16(9):1107-1115.
31. Zhang ZF, Morgenstern H, Spitz MR, et al. Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck. *Cancer Epidemiology, Biomarkers & Prevention.* 1999;8:1071-1078.
32. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2006;15(10):1829-1834.
33. Anantharaman D, Gheit T, Waterboer T, et al. Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. *J Natl Cancer Inst.* 2013;105(8):536-545.
34. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):467-475.
35. Katzel JA, Merchant M, Chaturvedi AK, Silverberg MJ. Contribution of demographic and behavioral factors on the changing incidence rates of oropharyngeal and oral cavity cancers in northern California. *Cancer Epidemiol Biomarkers Prev.* 2015;24(6):978-984.
36. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294-4301.
37. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst.* 2007;99(23):1801-1810.
38. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. *N Engl J Med.* 2007;356:1944-1956.
39. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst.* 2008;100(6):407-420.
40. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol.* 2014;50(5):380-386.
41. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9(1):e86023.
42. Zevallos JP, Mazul AL, Rodriguez N, et al. Previous tonsillectomy modifies odds of tonsil and base of tongue cancer. *Br J Cancer.* 2016;114(7):832-838.
43. Dahlstrom KR, Li G, Tortolero-Luna G, Wei Q, Sturgis EM. Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites. *Head Neck.* 2011;33(6):847-855.
44. Chaturvedi AK, Graubard BI, Broutian T, et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. *Cancer Res.* 2015;75(12):2468-2477.

45. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol.* 2012;22(2):128-142.
46. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. *Oral Oncol.* 2014;50(6):565-574.
47. Dahlgren L, Dahlstrand HM, Lindquist D, et al. Human papillomavirus is more common in base of tongue than in mobile tongue cancer and is a favorable prognostic factor in base of tongue cancer patients. *Int J Cancer.* 2004;112(6):1015-1019.
48. Dahlstrand H, Nasman A, Romanitan M, Lindquist D, Ramqvist T, Dalianis T. Human Papillomavirus Accounts both for Increased Incidence and Better Prognosis in Tonsillar Cancer. *Anticancer Research.* 2008;28:1133-1138.
49. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol.* 2006;24(17):2606-2611.
50. Goodman MT, Saraiya M, Thompson TD, et al. Human papillomavirus genotype and oropharynx cancer survival in the United States of America. *Eur J Cancer.* 2015;51(18):2759-2767.
51. Salazar CR, Anayannis N, Smith RV, et al. Combined P16 and human papillomavirus testing predicts head and neck cancer survival. *Int J Cancer.* 2014;135(10):2404-2412.
52. Tahtali A, Hey C, Geissler C, et al. HPV Status and Overall Survival of Patients with Oropharyngeal Squamous Cell Carcinoma – A Retrospective Study of a German Head and Neck Cancer Center. *Anticancer Research.* 2013;33:3481-3486.
53. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part C: Arsenic, metals, fibres, and dusts.* Vol 100C; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
54. Marchand JL, Luce D, Leclerc A, et al. Laryngeal and Hypopharyngeal Cancer and Occupational Exposure to Asbestos and Man-Made Vitreous Fibers: Results of a Case-Control Study. *American Journal of Industrial Medicine.* 2000;37:581-589.
55. Luce D, Leclerc A, Begin D, et al. Sinonasal Cancer and Occupational Exposures: A Pooled Analysis of 12 Case-Control Studies. *Cancer Causes & Control.* 2002;13(2):147-157.
56. Purdue M, Jarvholm B, Bergdahl IA, Hayes RB, Baris D. Occupational exposures and head and neck cancers among Swedish construction workers. *Scandinavian Journal of Work, Environment & Health.* 2006;32(4):270-275.
57. Langevin SM, O'Sullivan MH, Valerio JL, et al. Occupational asbestos exposure is associated with pharyngeal squamous cell carcinoma in men from the greater Boston area. *Occup Environ Med.* 2013;70(12):858-863.
58. Menvielle G, Fayosse A, Radoi L, et al. The joint effect of asbestos exposure, tobacco smoking and alcohol drinking on laryngeal cancer risk: evidence from the French population-based case-control study, ICARE. *Occup Environ Med.* 2016;73(1):28-33.

59. Demers PA, Kogevinas M, Boffetta P, et al. Wood Dust and Sino-Nasal Cancer: Pooled Reanalysis of Twelve Case-Control Studies. *American Journal of Industrial Medicine.* 1995;28:151-166.
60. d'Errico A, Pasian S, Baratti A, et al. A case-control study on occupational risk factors for sino-nasal cancer. *Occup Environ Med.* 2009;66(7):448-455.
61. Langevin SM, McClean MD, Michaud DS, Eliot M, Nelson HH, Kelsey KT. Occupational dust exposure and head and neck squamous cell carcinoma risk in a population-based case-control study conducted in the greater Boston area. *Cancer Med.* 2013;2(6):978-986.
62. Lippmann M, Cohen MD, Chen LC. Health effects of World Trade Center (WTC) Dust: An unprecedented disaster's inadequate risk management. *Crit Rev Toxicol.* 2015;45(6):492-530.
63. Dasaro CR, Holden WL, Berman KD, et al. Cohort Profile: World Trade Center Health Program General Responder Cohort. *Int J Epidemiol.* 2017;46(2):e9.
64. Centers for Disease Control and Prevention - World Trade Center Health Program. World Trade Center Health Program - Annual Status as of 12/31/2016. 2017; https://www.cdc.gov/wtc/pdfs/reports/wtchp_stats20161231-508.pdf. Accessed March 1, 2019.
65. Solan S, Wallenstein S, Shapiro M, et al. Cancer incidence in world trade center rescue and recovery workers, 2001-2008. *Environ Health Perspect.* 2013;121(6):699-704.
66. Li JH, Cone JE, Kahn AR, et al. Association Between World Trade Center Exposure and Excess Cancer Risk. *JAMA.* 2012;308(23):2479-2488.
67. Zeig-Owens R, Webber MP, Hall CB, et al. Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study. *Lancet.* 2011;378(9794):898-905.
68. Graber JM, Chuang CT, Ward CL, Black K, Udasin IG. Head and Neck Cancer in World Trade Center Responders: A Case Series. *J Occup Environ Med.* 2018;60(9):e439-e444.
69. Graber JM, Harris G, Black K, et al. Excess HPV-related head and neck cancer in the world trade center health program general responder cohort. *Int J Cancer.* 2018.
70. Boffetta P, Zeig-Owens R, Wallenstein S, et al. Cancer in World Trade Center responders: Findings from multiple cohorts and options for future study. *Am J Ind Med.* 2016;59(2):96-105.

DEVELOPMENT AND RELIABILITY OF A QUESTIONNAIRE DESIGNED TO RETROSPECTIVELY ASSESS RISK FACTORS FOR HEAD AND NECK CANCER AMONG WORLD TRADE CENTER GENERAL RESPONDERS

By

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Manuscript 1 of 3 of a dissertation entitled

MEASUREMENT AND EVALUATION OF RISK FACTORS FOR

CANCERS OF THE HEAD AND NECK IN A COHORT OF

9/11 WORLD TRADE CENTER RESPONDERS

Submitted to the

School of Public Health

And the

Graduate School – New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Written under the direction of

Judith M. Graber, PhD, MS

ABSTRACT

Background: We developed a risk factor assessment questionnaire designed to reconstruct behavioral risk factors for head and neck cancer (HNC) over the lifetime and relative to the 9/11 World Trade Center (WTC) response. The overall objective of this study was to assess the reliability between risk factor and exposure information collected by our questionnaire and that previously collected during WTC Health Program (WTCHP) monitoring visits.

Methods: We assessed face and content validity and cultural appropriateness through expert review and cognitive interviewing. Trained interviewers administered the survey by telephone, and participants had the option to complete the survey online. After data collection, we assessed agreement between our questionnaire results and data collected previously during WTCHP monitoring for constructs common to both data sources, including measures of smoking, alcohol consumption, and occupational exposures. We tested agreement between categorical variables using Cohen's Kappa (K) and between continuous variables using intraclass correlation coefficient (ICC). We additionally compared agreement statistics by disease status, survey mode, and year of WTCHP enrollment.

Results: We observed near perfect agreement between ever smoking measures overall and during each study period (all $K > 0.85$) and for overall, pre-WTC, and post-WTC years of smoking. There was moderate agreement between measures of smoking frequency and duration. Agreement between measures of smoking frequency, but not duration, differed by disease status, and agreement between smoking measures was higher for participants who completed our survey by phone than for those who self-

administered online. There were no differences based on enrollment before vs. after diagnosis (among cases only).

Conclusion: There is potential for reporting bias and a mode effect that should be considered when interpreting results of future studies that use this questionnaire; however differential misclassification appears to be minimal. Our questionnaire may be useful for future studies examining similar behavioral risk factors among WTC-exposed populations.

INTRODUCTION

People involved in the World Trade Center (WTC) rescue, recovery, and cleanup efforts following the collapse of the WTC towers on September 11, 2001 (9/11) faced potential exposure to multiple known and suspected human carcinogens.[1-3] As such, WTC-related exposures may place responders at increased risk for adverse health outcomes, including cancer. Indeed, studies have found excess incidence of all and certain cancer sites, including cancers of the prostate and thyroid, among WTC-exposed persons.[4,5] As well, a 40% excess incidence (standardized incidence ratio [SIR]: 1.40, 95% confidence interval [CI]: 1.01, 1.89) of head and neck cancers (HNCs) diagnosed between 2009 and 2012 has been reported among members of the WTC Health Program (WTCHP) General Responder Cohort (GRC). However, other population-level behavioral risk factors, including tobacco use, alcohol consumption, and increased sexual activity (an established indicator of persistent human papillomavirus [HPV] infection risk[6-8]),[6,9-13] may play a role in the etiology of HNC in this population. Given that risk behaviors may change over time or after traumatic events (such as participation in the WTC response), reconstruction of these factors over the course of the lifetime, including before, during, and after the WTC exposure period, is critical to assess the association between WTC exposures and HNC.

The WTC health program (WTCHP) provides medical monitoring and treatment for certified conditions to eligible WTC responders.[14] WTCHP GRC members receive an initial physical examination and undergo annual health monitoring visits thereafter. The WTCHP General Responder Data Center (GRDC) in the Icahn School of Medicine at Mount Sinai in New York City maintains data collected from consenting GRC members during enrollment and follow-up. This includes clinical, questionnaire, and WTC exposure information, which can be available for research purposes. Although the WTCHP collects a wealth of information, the utility of these data for research about HNC is limited, because the enrollment and annual health questionnaires were designed for medical monitoring, not research. For example, most questions about alcohol use concerned current consumption, making it difficult to reconstruct this risk behavior over the lifetime. Moreover, several potential risk factors for HNC, including smokeless tobacco, marijuana use, and sexual behavior, were not assessed at all, further necessitating the need for to develop a retrospective exposure assessment tool.

As part of a larger case-control study of HNC (WTC Cancer Risk Epidemiology Study, WTC-CARES), we developed a risk factor assessment questionnaire designed to reconstruct lifetime exposure to tobacco, alcohol, and marijuana use, as well as tooth loss and sexual history (as surrogate measure of HPV risk). Although we developed questions based on previous studies, it is important to assess validity and reliability of study questionnaires to the extent possible. As such, the overall objective of this study was to assess the reliability between risk factor and exposure information collected as part of the WTC-CARES study and that previously collected during WTCHP monitoring visits.

METHODOLOGY

Study Population

This research utilizes data collected from participants of WTC-CARES, a nested case-control study of WTCHP GRC members. Cases (n=64) were GRC members with a diagnosis of HNC, and controls (n=136) were GRC members without cancer, identified via risk-set sampling and then individually matched 2-to-1 on age, sex, and race/ethnicity. Selected participants were mailed a letter with information about the study and how to schedule a telephone interview or complete the survey online. See Manuscript 2 for additional details about WTC-CARES participant selection and recruitment.

The WTC-CARES Questionnaire

Question Selection

Development of the WTC-CARES questionnaire was informed by standardized survey questions, including the National Health Interview Survey (NHIS),[15] the Behavioral Risk Factor Surveillance System (BRFSS),[16] and the Tobacco Use Supplement to the Current Population Survey (TUS-CPS),[17] as well as an extensive literature review of other studies that assessed cancer risk factors via questionnaire. In addition to descriptions of study instruments in published manuscripts and questionnaires provided as supplemental material to published works, we requested and reviewed study questionnaires from two other case-control studies of HNC (Collaborative Study of Head and Neck Diseases [CoHANDS][18] and Carolina Head and Neck Caner Epidemiology [CHANCE][19]) to see how they assessed lifetime risk factor behaviors. In particular, we examined (1) if and how lifetime risk factor behaviors were measured, given that such behaviors may change over the course of a lifetime, and (2) how use of non-cigarette tobacco products, marijuana, sexual behavior, and oral health were assessed, given that these are not assessed by the WTCHP. Although informative in terms of question content and structure, none of these studies had attempted to reconstruct lifetime risk behaviors at times relative to a specific event such as the WTC response period. Adaptation, review, and testing of the resulting study instrument was therefore critical.

Expert Review and Cognitive Testing

We assessed face and content validity, as well as cultural appropriateness, through expert review and cognitive interviewing with members of the target population, in this case, members of the GRC. Reviewers were colleagues and/or collaborators of the study investigators and included: 2 WTCHP clinicians who work with GRC members; a medical internist and tobacco treatment expert; an infectious cancer epidemiologist and HPV expert; 2 oncologists; 2 cancer epidemiologists from the New Jersey State Cancer Registry (NJSCR); an occupational epidemiologist; and a survey methodologist. We emailed reviewers a copy of the draft questionnaire, asking for comments and suggestions to improve the face and content validity, and made revisions based on their input.

We then tested the revised draft using cognitive interviewing procedures. Cognitive interviewing is a technique used to study the process through which a respondent interprets a question and formulates his or her response. Specifically, a cognitive interview assesses question comprehension (how the respondent interprets the question), recall (how the respondent searches memory for relevant information), judgement (how the respondent evaluates and estimates the response) and response (does the respondent provide information in the format requested).[20] Interviews occur in “rounds” such that after completing several interviews, the questionnaire is revised based on findings and retested in subsequent rounds with different participants. This process continues until no additional problems are identified.[21] Though there is no set rule, typical cognitive interviewing protocols call for 3 to 4 iterative rounds of 5 to 10 interviews each. However, given limited resources, we employed an abbreviated approach similar to that described by Spark and Willis.[22] We conducted 4 rounds of 3 interviews each for a total of 12 interviews. Interview participants included 3 GRC members who had cancer (not HNC), 6 GRC members without cancer, and 3 non-WTC-exposed cancer patients. We recruited GRC participants from the WTC Cancer Clinic at Rutgers in Piscataway, New Jersey and non-WTC-exposed participants from the Rutgers Tobacco Dependence Program in New Brunswick, New Jersey.

We employed a hybrid interview approach, in which we prospectively administered the interview and simultaneously probed the respondent to assess comprehension, recall, judgement, and response. Examples of probes include "what does 'regularly' mean to you?" to assess comprehension and "how did you arrive at your answer?" to assess recall and judgment. Of note, we learned (1) both GRC members and non-WTC-exposed cancer patients had good recall of tobacco, alcohol, and marijuana use relative to the WTC response period; (2) GRC members did not feel confident in their ability to accurately report exposure to specific environmental exposures, such as asbestos, during the WTC response period, as they assumed they were exposed to "everything"; (3) GRC interviewees exhibited emotional responses to questions about external exposures (e.g., asbestos) during the WTC response period, but not to questions about behavioral exposures (e.g., tobacco) during the same period; and (4) GRC interviewees felt more comfortable being honest about their risk behaviors when they understood why they were being assessed. As a result of findings (2) and (3), we opted not to ask GRC members about environmental exposures during the WTC response period. Because of finding (4), we added a statement to the survey introduction to provide some explanation for risk behavior question and assure confidentiality, which performed well in the final round of interviews:

> *For this study, we will be asking detailed questions about certain behaviors, such as tobacco and alcohol use, because we are trying to see if they are associated with head and neck cancers. We know that this information is personal, but your honest answers to our questions are important for learning more about these types of cancers. As a reminder, this study has been given a Certificate of Confidentiality, which means we cannot share anything you tell us with anyone, even if a court orders us to do so, without your explicit permission.*

Final Instrument and Data Collection

The final WTC-CARES questionnaire assessed tobacco (cigarette, cigar, smokeless tobacco, hookah, pipe) use, alcohol use, marijuana use, and environmental exposures (e.g., asbestos, dusts) during each of 3 time periods: (1) before September 11^{th} 2001, (2) during the time that the participant worked or volunteered on the WTC response efforts (except for environmental exposures), and (3) subsequently until the time of case HNC diagnosis (Figure 1). It additionally includes measures of oral health (i.e., tooth loss before and after 9/11, tonsillectomy), sexual history (i.e., age of sexual debut, number of sexual partners during each of the 3 time periods, history of a sexually transmitted infection, receipt of HPV vaccine), and mental health treatment (i.e., years of treatment episodes). See Figures 2a and 2b for an outline of questionnaire items.

Trained interviewers administered the WTC-CARES survey by telephone; alternatively, participants could complete the survey online. Though not the preferred mode of data collection, we offered a web-based option, because common sequelae of HNC include speech difficulty. We took substantial care to minimize differences between survey modes. For example, the interviewer- and self-administered surveys were identical with respect to text and supplemental information, and the interviewers were specially trained to avoid script deviations. Data collection occurred from July 2017 through April 2018, after which we received deidentified survey data with a unique identification (ID) number.

The WTCHP Questionnaires

GRC members receive an annual health monitoring exam, which includes a clinical exam as well as self-reported assessment of physical, mental, and behavioral health. At the first visit, members complete the Exposure Assessment Questionnaire (EAQ), the Self-Administered Medical Questionnaire (SAMQ), the Mental Health Screening Questionnaire (MHSQ), and the Interviewer-Administered Medical Questionnaire in addition to a physical examination. At subsequent visits, members complete a modified IAMQ, the Self-Administered Mental Health Questionnaire (SAMHQ), the Diagnostic Interview Schedule (DIS), and a physical examination. See Figure 3 for a description of each WTCHP questionnaire.

The initial questionnaires include items about occupational and environmental exposures during participation in the WTC response and as associated with other occupations or hobbies, lifetime cigarette smoking (i.e., ever, age first smoked, current, age last smoked, cigarettes per day), ever and current cigar smoking, ever and current pipe smoking, and current alcohol consumption. The periodic questionnaires include assessments of occupational and environmental exposures (since previous exam), lifetime cigarette smoking (for members who were never or former smokers at previous exam: ever, current, age last smoked, cigarettes per day), current cigarette smoking, ever and current cigar smoking, ever and current pipe smoking, and current alcohol consumption.

We obtained deidentified data from the WTCHP for all WTC-CARES participants. For participants who enrolled in the GRC prior to HNC diagnosis (for controls, this was the diagnosis for the matched case), we included data from all monitoring visits up to and including the year of diagnosis for reconstruction of risk behaviors. For participants who enrolled after the HNC diagnosis, we considered only data from the first monitoring visit.

Measures

Tobacco Use

Both WTC-CARES and WTCHP questionnaires assessed lifetime ever cigarette smoking by asking participants if they had smoked at least 100 cigarettes. For WTC-CARES, we separately assessed smoking prior to, during, and after the WTC responses, and thus determined ever, duration, and intensity of smoking during each study period based on responses to the period-specific questions. For each study period, we also asked if there was a period of more than 1 year during which the participant did not smoke at all and accounted for this when calculating duration of smoking. For WTCHP, we inferred ever and duration smoking during each study period based on the age of smoking initiation provided at visit one and the smoking status (and age of smoking cessation, if applicable) at the monitoring visit closest to (but not exceeding) the year of HNC diagnosis. For example, if a participant was 40 on 9/11 and reported first smoking cigarettes at age 20, we inferred that they smoked continuously for 20 years during the pre-WTC study period. Without additional information about changes in smoking frequency or intensity over the lifetime, we assumed a constant smoking intensity (i.e., cigarettes per day). For example, if a participant was 40 in 2001 and reported smoking 20 cigarettes per day at the monitoring visit in 2015, we assumed they had been smoking 20 cigarettes per day for 14 years during the post-WTC study period.

Alcohol Consumption

As with tobacco use, the WTC-CARES questionnaire separately assessed alcohol consumption during each of the three study periods and determined ever, duration, and intensity of drinking based on responses to the period-specific questions. For WTCHP, only current alcohol consumption was assessed at baseline and follow-up visits, thus ever drinking during the post-WTC study period was inferred if a participant indicated any alcohol consumption during an applicable monitoring visit (i.e., up to and including year of HNC diagnosis). Although the WTCHP questionnaire did assess intensity of drinking (drinks per week), these questions were frequently left blank; thus, only ever/never current consumption could be inferred.

Occupational Exposures

Like the behavioral exposures, the WTC-CARES questionnaire included study period-specific questions (e.g., BEFORE 9/11, were you EVER exposed to asbestos? [yes/no]). As such, occupational exposures were determined directly based on answers to period specific questions. The WTCHP assessed occupational exposures in the context of each specific occupation or hobby a participant reported (e.g., When you worked as a <trade/profession> between the years of <years in trade/profession>, were you exposed to any of the following? …asbestos [yes/no]) If a participant indicated exposure, we then inferred exposure during specific study periods based on the first and last year a participant worked at that occupation. For example, if a participant had a particular occupation from 1990 until 2000 and reported having been exposed to asbestos while in that occupation, we inferred that they had been exposed to asbestos during the pre-WTC time period only.

See Figure 4 for a comparison of question wording across data sources.

Protection of Human Subjects

The Health Sciences Institutional Review Board at Rutgers University reviewed and approved the study protocol, including recruitment, consent, and data collection procedures (Pro20160001045). This included details of an Honest Broker agreement, whereby a designated entity maintained all protected health information (PHI) for WTC-CARES. We received only deidentified survey data that included a unique ID number, and the WTCHP data we obtained from the GRDC included the same ID number. We then merged the two data sources by this variable. The Honest Broker agreement was also outlined in our Data Use Agreement (DUA) between Rutgers University and the GRDC. We additionally obtained a certificate of confidentiality from the CDC.

Statistical Analysis

We assessed agreement by data source for each construct assessed by both WTC-CARES and WTCHP. For categorical measures we estimated agreement using Cohen's Kappa (K) statistic,[23] considering estimates less than 0, 0 to 0.2, 0.21 to 0.4, 0.41 to 0.6, 0.61 to 0.8, and greater than 0.8 indicative of "poor," "slight," "fair," "moderate," "substantial," and "near perfect" agreement, respectively.[24] For continuous measures, we estimated agreement using intraclass correlation coefficient (ICC), using absolute agreement 2-way mixed models, considering estimates less than 0.5, 0.5 to less than 0.75, 0.75 to less than 0.9, and greater than 0.9 indicative of "poor," "moderate," "good," and "excellent" reliability.[25,26] For risk factor measures, we further compared agreement estimates by case/control status, and, among cases, year of GRC enrollment (before vs. after year of diagnosis) with non-overlapping 95% confidence intervals considered indicative of statistical significance. Additional sensitivity analyses included comparison of agreement of behavioral risk factor measures by WTC-CARES survey mode (telephone vs. web), by enrollment before 2007 (median year of enrollment) vs. 2007 or later, and occupation. To assess potential selection bias, we also compared risk behaviors, as measured by WTCHP, for cases who enrolled in WTC-CARES and cases who did not enroll, using 2-sided chi-square tests and t-tests for categorical and continuous measures, respectively.

We performed all analysis using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and SPSS 24 (IBM Corp, Armonk, New York, USA) software packages.

RESULTS

Two hundred WTC-CARES participants, including 64 cases and 136 controls, contributed to analysis. Most participants were male (88.5%) and on average 41.7 years old (standard deviation [SD]: 6.8) on 9/11 and 48.2 years old (SD: 8.3) at enrollment in the GRC (Table 1). Cases were slightly older than controls at enrollment, but gender distributions were similar across study groups. The majority of participants were non-Hispanic white (69.2%) and had protective services occupations (51.0%).

We observed near perfect agreement between ever smoking measures overall and during each study period (all K > 0.85) and for overall, pre-WTC, and post-WTC years of smoking; however, we observed lower agreement for duration of smoking during the WTC response period (K=0.5; Table 2). With respect to smoking intensity (cigarettes per day) during each study period, we observed moderate agreement, with higher prevalence estimates from WTCHP than WTC-CARES. When WTCHP-assessed ever smoking was stratified by reported smoking status at the time of the WTC-CARES survey, we found that four (5.4%) of 74 former smokers did not report ever smoking during a WTCHP monitoring visit, while 7 of 111 (6.3%) of "never smokers" had reported ever smoking during a monitoring visit (data not shown). Among those reporting current smoking to WTC-CARES (n=15), all reported smoking during a WTCHP monitoring visit.

Conversely to what we observed for smoking, WTC-CARES yielded higher post-WTC alcohol drinking prevalence (77.0% vs. 73.7%) and agreed moderately with

WTCHP estimates (K=0.51). By occupational group, agreement was somewhat lower for those in the protective services as opposed to other occupations (K=0.42 [95%CI: 0.20, 0.64] vs. K=0.58 [95% CI: 0.40, 0.76], data not shown), although this difference was not statistically significant. Agreement between alcohol measures was higher for cases enrolled prior to diagnosis as opposed to after (K=0.69 [95% CI: 0.45, 0.94] vs. K=0.21 [95% CI: -0.17, 0.60]), but this difference was not statistically significant.

We observed poor to fair agreement when comparing occupational exposures during the pre- and post-WTC study periods with WTCHP generally producing higher prevalence estimates; however, we also note considerable missingness in the WTCHP data.

In general, we saw no differences in agreement for risk factors by HNC status, with the exception of cigarette smoking intensity (Table 3). Agreement was significantly higher for cases when considering the pre-WTC study period (ICC=0.80 [95% CI 0.67, 0.88] for cases vs. ICC=0.55, [95% CI 0.41, 0.66] for controls) but significantly higher for controls when considering the post-WTC period (ICC=0.52 [95% CI 0.36, 0.71] for cases vs. ICC=0.82, [95% CI 0.75, 0.87] for controls). Among the occupational exposures, only agreement when assessing diesel/gasoline exhaust exposure differed by case/control status. During both pre- and post-WTC periods, agreement was very poor for cases but fair for controls. Comparing cases enrolled before vs. after HNC diagnosis, we saw no significant differences in agreement of behavioral risk factor and occupational exposure measures (Table 4).

Agreement between measures of ever cigarette smoking, overall and during each study period, was substantial to near perfect for both survey modes (Table 5). For measures of smoking duration, agreement was generally higher for the telephone survey than the web survey, though none of these differences were statistically significant. Agreement was also higher for the telephone group when comparing measures of average cigarette consumption prior to and during WTC exposure, and these differences were statistically significant. There were no differences in agreement post-WTC alcohol consumption by survey mode.

Agreement between measures of post-WTC smoking prevalence and during-WTC smoking intensity was significantly higher among those who enrolled in the GRC in 2007 or after, as opposed to before 2007 (Table 6). There were no other differences in agreement when comparing by enrollment year.

Among cases, WTCHP-assessed smoking and drinking did not differ by WTC-CARES enrollment status (Table 7).

DISCUSSION

As part of a case-control study of HNC within the WTCHP GRC, we developed a questionnaire to retrospectively assess risk factors before, during, and after WTC exposure. We compared occupational and behavioral risk factor data from our WTC-CARES questionnaire to that collected previously by the WTCHP and found substantial to near perfect agreement between measures of ever smoking during all study periods. We also observed good to excellent agreement between measures of lifetime, pre-WTC, and post-WTC smoking duration and between measures of post-WTC smoking intensity. Agreement was fair to moderate for measures of smoking duration during the WTC response, smoking intensity during and after the WTC response, and ever alcohol consumption after the WTC response. Conversely, agreement between measures of occupational exposures before and after the WTC response was generally poor.

We expected high agreement for measures of ever smoking, given the nearly identical wording of the WTC-CARES and WTCHP ever-smoking questions; however, we did not anticipate that the WTCHP measure would yield slightly higher smoking prevalence estimates. Potential explanations for this finding include increasing reluctance of former smokers to report having ever smoked, as social acceptability of smoking has declined over time. For example, a participant may have been willing to admit having smoked upon enrollment in the GRC 10 or more years ago than in 2017 when WTC-CARES data collection occurred. Indeed, about 6% of participants who reported never smoking in WTC-CARES had reported ever smoking in the WTCHP, whereas all who reported current smoking in WTC-CARES also reported smoking in the WTCHP. Moreover, we observed higher agreement of lifetime smoking measures among those enrolled in 2007 or later than among those enrolled prior to 2007. Although these differences were not statistically significant, they suggest that social desirability bias may explain why our WTC-CARES questionnaire yielded slightly lower smoking estimates.

We expected some disagreement between measures of smoking duration. The WTC-CARES questionnaire separately assessed years of smoking during each study period and accounted for any time when a participant was not smoking, whereas we inferred smoking duration in the WTCHP data as continuous between ages of first and last use. This may explain the higher average durations estimated by the WTCHP data. We also expected less agreement between measures of smoking intensity during each study period, because only the WTC-CARES questionnaire asked about consumption during each time, while the WTCHP questionnaires asked only about current (for current smokers) or lifetime average (for former smokers). Thus, we had to assume that a current smoker's daily consumption was constant across all years of smoking, which may not be accurate. This may explain why the WTCHP data yielded higher consumption estimates.

We can offer two potential explanations for our observation of only fair to moderate agreement between measures of post-WTC alcohol drinking. First, only one version of the WTCHP baseline (visit one) IAMQ included a question about lifetime consumption, thus for consistency across participants we could only consider measures of current (at the time of the monitoring visit) drinking. A participant's reported drinking status at the time of a monitoring visit is likely not reflective of the entire post-WTC (until case diagnosis) period. Second, participants, many of whom were law enforcement officers, may have underreported alcohol consumption during a monitoring visit. A sensitivity analysis finding somewhat lower agreement between WTC-CARES and WTCHP alcohol measures among those in the protective services supports this notion.

We did not anticipate such poor agreement between measures of occupational exposures, given that the question wording was relatively similar across instruments. However, we noted substantial missingness in the WTCHP measures of occupational exposures, ranging from 16.5% to 18.5% depending on the exposure, which may contribute to some of the discrepancies across measures. Additionally, although wording of the questions themselves were similar, their contexts were different. The WTC-CARES questionnaire asked about each exposure relative to the WTC response (before or after), while the WTCHP asked about exposures within reported occupations (during the time they had a particular job or hobby). Since occupation timelines do not necessarily align with the WTC-CARES study periods, the WTCHP approach may not be adequate for reconstructing exposures relative to the WTC response period.

Given the potential for recall bias in case-control studies, establishing agreement between current and previously-administered self-reported risk behaviors when possible may alleviate concerns about misclassification.[27,28] In our study, recall bias may exist if cases and controls experience differential recall of exposures or risk factor behaviors. In this instance, cases might report their past behaviors differently when surveyed before as opposed to after diagnosis. When comparing WTC-CARES responses to pre-diagnosis WTCHP data among cases, we found substantial to near perfect agreement between ever smoking and drinking measures, which should alleviate concerns about recall bias in our case-control study.

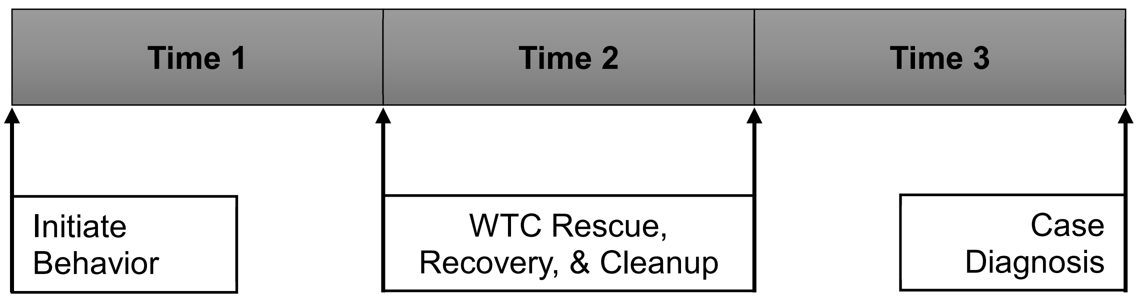
While there were no differences in agreement by survey mode for ever and years of smoking, we observed higher agreement for two cigarette intensity measures among those who completed WTC-CARES by telephone, suggesting that certain analyses of WTC-CARES data may be subject to a mode effect. As such, future analysis of this data should include an assessment of survey mode and adjust for mode if necessary.

We have several limitations to note. Reconstruction of WTCHP risk behavior data relative to the WTC exposure period was challenging, due both to some key information not being collected (e.g., changes in tobacco use, frequency, or intensity over the lifetime), as well as the subjective nature of some questions (e.g., “Over the years, do you consider yourself a Non-drinker, Occasional drinker, Moderate drinker, or Heavy drinker?”). Decisions made when creating equivalent constructs in each dataset may have contributed to differences between estimates produced by WTCHP and WTC-CARES questionnaires. Whereas our WTC-CARES questionnaire specifically asked about behavior frequency and duration during each study period (before, during, and after the WTC response), the WTCHP asked only about lifetime or current behaviors. As such, we inferred behavior for each study period based on peripheral information. For example, for a current smoker, we had to assume that smoking intensity during the pre-WTC period was the same as that reported upon GRC enrollment, which may not be accurate. However, finding that risk behaviors cannot be easily or adequately reconstructed relative to the WTC response period demonstrates the necessity of developing our own questionnaire for WTC-CARES.

Additionally, our results should be considered in light of the small sample size, which resulted in wide confidence intervals when comparing agreement estimates by subgroup. This suggests that even null findings may be the result of inadequate power, rather than lack of association. Potential selection bias is of additional concern, if the distribution of HNC risk factors differs among people who enrolled in WTC-CARES differs from those whom we selected but did not enroll (e.g., refused). However, we found no differences in smoking or alcohol consumption by WTC-CARES enrollment status, suggesting minimal selection in the present analysis. Finally, we were not able to assess agreement for measures of other risk factors assessed by the WTC-CARES questionnaire (e.g., sexual behavior, heavy alcohol consumption), because they were either not assessed by the WTCHP or had too many missing responses in the WTCHP dataset.

Despite these limitations, our study has important findings. By demonstrating high reliability with smoking measured prior to diagnosis, we alleviate some concerns for recall bias in WTC-CARES. Our results also highlight the importance of question context by showing poor agreement between occupational exposure questions of similar wording but different format. We also found some evidence of reporting bias in this population, as well as a potential mode effect, which we should be mindful of when interpreting results of the WTC-CARES case-control study, as well as other studies among WTC-exposed populations. Finally, our results demonstrate that while the WTCHP monitoring data includes comprehensive WTC exposure information, assessment of lifetime risk behaviors among WTC-exposed persons requires additional measures. Our questionnaire may be useful for other studies of cancer outcomes in this unique population.

Figure 1. WTC-CARES Study Periods*



*Length of each period varies by individual and is not drawn to scale

Figure 2a: Assessment of tobacco, alcohol, and marijuana use, WTC-CARES survey

Study period	Construct	Assessment Question
Lifetime	Ever Use	Have you [used] at least [##] [products] in your entire life?
	Age First Use	How old were you when you FIRST started [using product]?
	Current Use	Do you now [use product] every day, some days, rarely, or not at all?
	Age Last Use	How old were you when you LAST [used product]?
Before WTC	Frequency	Before 9/11, when you were [using product], did you usually [use]… 1 Every day 2 One or more days per week 3 One or more days per month 4 One or more days per year 5 Less than once a year On average, how many days per week/month/year did you [use product]?
	Intensity	On average, how many [products] did you usually [use] per day? During that time, on days that you [used products], how many did you usually [use]?
	Years of Non-Use	[Before 9/11] was there ever a period of 1 year or longer that you did NOT [use product] at all? Still thinking about that time frame, for how many TOTAL YEARS did you NOT [use product] AT ALL?
During WTC	Frequency	[During WTC response period], when you were [using product], did you usually [use]… 1 Every day 2 One or more days per week 3 One or more days per month 4 One or more days per year 5 Less than once a year On average, how many days per week/month/year did you [use product]?
	Intensity	On average, how many [products] did you usually [use] per day?

Study period	Construct	Assessment Question
		During that time, on days that you [used products], how many did you usually [use]?
	Change in Use	Thinking about your life [during WTC response period], would you say your [product use] increased, decreased, or stayed about the same, relative to times BEFORE [WTC response period]?
After WTC	Frequency	Between [WTC response period] and [CANCER_DATE], when you were [using product], did you usually [use]… 1 Every day 2 One or more days per week 3 One or more days per month 4 One or more days per year 5 Less than once a year On average, how many days per week/month/year did you [use product]?
	Intensity	On average, how many [products] did you usually [use] per day? During that time, on days that you [used products], how many did you usually [use]?
	Change in Use	Thinking about your life AFTER [WTC response period], would you say your [product use] increased, decreased, or stayed about the same, relative to times BEFORE [WTC response period]? For low long did this increase/decrease last?
	Years of Non-Use	[Between WTC response period and CANCER_DATE] was there ever a period of 1 year or longer that you did NOT [use product] at all? Still thinking about that time frame, for how many TOTAL YEARS did you NOT [use product] AT ALL?

Figure 2b: Assessment of tooth loss, tonsillectomy, and sexual behavior measures, WTC-CARES survey

Construct	Assessment Question
Tooth Loss	• Have you ever had any permanent teeth extracted due to gum disease, gingivitis, or decay? • How many permanent teeth did you have extracted before September 11, 2001? • How many permanent teeth did you have extracted between Nine-Eleven and [CANCER_DATE]?
Tonsillectomy	• Have you had your tonsils removed? • How old were you when you had your tonsils removed?
Sexual Behavior History	• Have you ever had sex? By 'sex' we mean sexual intercourse, oral sex, or anal sex. • How old were you when you had sex for the FIRST time? • In your entire life, how many different sexual partners have you had? Please count every partner, even those you were with only once. • Before Nine-Eleven, how many different sexual partners did you have? Please count every partner, even those you were with only once. • Between [EXP. START] and [EXP. END], how many different sexual partners did you have? Please count every partner, even those you were with only once. • Between [EXP. END] and [CANCER DATE], how many different sexual partners did you have? Please count every partner, even those you were with only once. 0 0 partners 1 1 partner 2 2 to 5 partners 3 6 to 10 partners 4 11 to 15 partners 5 16 to 25 partners 6 26 to 50 partners 7 51 to 100 partners 8 More than 100 partners
STI Diagnosis	Have you ever been diagnosed with a sexually transmitted disease or infection by a doctor or health care provider?
HPV Vaccine	• Have you ever received an HPV shot or vaccine? • How many HPV shots did you receive?

Figure 3: Description of World Trade Center Health Program Questionnaires*

Questionnaire	Description

EAQ	• Collected at the first monitoring visit only.
	• Interviewer-administered questionnaire
	• Assesses exposures to potentially harmful physical and psychological conditions from:
	  o Work before 9/11
	  o Work on the WTC recovery effort
	  o Current work
	• Assesses overall and specific exposures related to:
	  o Work on the WTC recovery effort
	  o Hygiene at the WTC site
	  o Use of personal protective equipment at the WTC site

IAMQ	• Collected at each monitoring visit.
	• Administered by a trained medical professional.
	• Structured, medical history questionnaire, gathers information about:
	  o Medical conditions (e.g. self-reported symptoms, diagnostic testing and diagnosed medical conditions)
	  o Alcohol and tobacco use

MHSQ	• Collected at first monitoring visit.
	• Primary focus is on self-reported mental health functioning.
	• Questions topics include:
	  o General health (SF-12 VR)
	  o Mental health symptoms (PTSD, panic disorder, generalized anxiety disorder, major depression)
	  o Alcohol use and life stressors

SAMQ	• Collected at second and subsequent monitoring visits.
	• Primary focus is on self-reported mental health functioning.
	• Questions topics include:
	  o General health (SF-12 VR)
	  o Mental health symptoms (PTSD, panic disorder, generalized anxiety disorder, major depression)
	  o Alcohol use and life stressors

PE	• Performed at each monitoring visit by a physician
	• Takes 20 min to complete, on average and includes:
	  o Measurements of height, weight, blood pressure, pulse rate, and respiration
	  o Musculoskeletal and neurological examinations
	  o Examination of ears, eyes, nose, sinuses, throat, neck, chest, heart, abdomen, extremities and skin.
	  o Findings are documented on a customized form.

*Adapted from Dasaro et al, 2015

Figure 4: Question Wording for Select Constructs, WTC-CARES vs. WTCHP

WTC-CARES Question(s)	WTC-HP Question(s)
Cigarette Smoking	
Have you smoked at least 100 cigarettes in your entire life?	Have you smoked at least 100 cigarettes (5 packs) in your entire life?
How old were you when you FIRST started smoking cigarettes fairly regularly?	How old were you when you started smoking cigarettes fairly regularly?
How old were you when you LAST smoked cigarettes?	How old were you when you last smoked cigarettes regularly?
[During study period], when you were smoking cigarettes, did you usually smoke… • Every day • One or more days per week • One or more days per month • One or more days per year • Less than once a year	When you smoked cigarettes regularly, how many cigarettes did you usually smoke per day?
[If not daily] On average, how many days per week/month/year did you smoke cigarettes?	On average, how many cigarettes do you now smoke per day?
On average, how many cigarettes did you usually smoke per day?	
[If not daily] During that time, on the days you smoked cigarettes, how many did you usually smoke?	

WTC-CARES Question(s)	WTC-HP Question(s)
Calculation of Smoking Duration	
Time 1, if continued to 9/11: [Age on 9/11] – [Age First Smoked] – [Years not smoking during that period] = Duration of Smoking, Pre-WTC	*Time 1, if continued to 9/11:* [Age on 9/11] – [Age First Smoked] = Duration of Smoking, Pre-WTC
Time 1, if stopped before 9/11: [Age Last Smoked] – [Age First Smoked] – [Years not smoking during that period] = Duration of Smoking, Pre-WTC	*Time 1, if stopped before 9/11:* [Age Last Smoked] – [Age First Smoked] = Duration of Smoking, Pre-WTC
Time 2: Duration of participation in WTC response = Duration of Smoking, During WTC response	*Time 2:* Duration of participation in WTC response = Duration of Smoking, During WTC response
Time 3, if stopped before case diagnosis: [Age Last Smoked] – [Age on 9/11 or Age First Smoked, if started after WTC response] – [Years not smoking during that period] = Duration of Smoking, Post-WTC	*Time 3, if stopped before case diagnosis:* [Age Last Smoked] – [Age on 9/11 or Age First Smoked, if started after WTC response] = Duration of Smoking, Post-WTC
Time 3, if continued to diagnosis: [Age at Case Diagnosis] – [Age on 9/11 or Age First Smoked, if started after WTC response] – [Years not smoking during that period] = Duration of Smoking, Post-WTC	*Time 3, if continued to diagnosis:* [Age at Case Diagnosis] – [Age on 9/11 or Age First Smoked, if started after WTC response] = Duration of Smoking, Post-WTC

<table>
<tr><th>WTC-CARES Question(s)</th><th>WTC-HP Question(s)</th></tr>
<tr><td colspan="2">Alcohol Consumption</td></tr>
<tr><td>In ANY ONE YEAR, have you had at least 12 drinks of any type of alcoholic beverage?

How old were you when you FIRST started drinking alcoholic beverages? Please do not include times when you had only a sip or two from a drink.

How old were you when you LAST had a drink of any type of alcoholic beverage?

[During study period] when you were drinking alcoholic beverages, did you usually drink…
• Every day
• One or more days per week
• One or more days per month
• One or more days per year
• Less than once a year

On average, how many days per week/month/year did you drink?

On average, how many alcoholic beverages did you usually drink per day?

During that time, on the days that you drank alcoholic beverages, how many did you usually drink?

[During study period], did you ever have 4/5 or more drinks of any type of alcoholic beverages in a single day?

During that time, about how often did you have 4/5 or more drinks in a single day?
• Same response options as above

On average, how many days per week/month/year did you have 4/5 or more drinks in a single day?</td><td>(Beginning mid-2010)
Describe your consumption of alcohol:
• None/non-drinker
• Less than one drink per week
• More than one drink per week

(Until mid-2010)
Over the years, do you consider yourself a:
• Non-drinker
• Occasional drinker
• Moderate drinker
• Heavy drinker
• I used to drink heavily, but quit ____ years/months/weeks ago</td></tr>
</table>

<table>
<tr><th>WTC-CARES Question(s)</th><th>WTC-HP Question(s)</th></tr>
<tr><td colspan="2">Occupational and Environmental Exposures</td></tr>
<tr><td>(For pre-WTC) BEFORE 9/11, were you EVER exposed to [substance]?

(For post-WTC) Between [last day on site] and [case diagnosis month and year], were you EVER exposed to [substance]?

(If yes) About how often were you exposed to [substance]?
• Every day
• A few times a week
• A few times a month
• A few times a year
• Less than once a year

For how long were you exposed to [substance] at that frequency?
_____ days/weeks/months/years</td><td>When you worked as a [trade] between the years of [period], were you ever exposed to any of the following?

If yes, for the years you did this trade, on average, how often would you say you were exposed?
• Incidental
• A few times a year
• A few times a month
• A few times a week
• Daily
• Don’t know</td></tr>
</table>

Table 1. Participant Characteristics (N=200)

	Overall N=200	Cases n=64	Controls n=136
Age on 9/11, mean ± SD	41.7 ± 6.8	41.9 ± 6.8	41.6 ± 6.8
Age at enrollment in WTCHP, mean ± SD	48.2 ± 8.3	51.1 ± 9.1	46.8 ± 7.5
Male sex, n (%)	177 (88.5)	57 (89.1)	120 (88.2)
Race/Ethnicity, n (%)			
Non-Hispanic white	137 (69.2)	52 (82.5)	85 (63.0)
Non-Hispanic black	24 (12.1)	*	*
Hispanic	31 (15.7)	8 (12.7)	23 (17.0)
Non-Hispanic other	5 (2.5)	0 (0)	5 (3.7)
Occupation, n (%)			
Protective Services	102 (51.0)	39 (60.9)	63 (46.3)
Construction	34 (17.0)	8 (12.5)	26 (19.1)
Mechanic/Machinist	8 (4.0)	*	*
Communications	16 (8.0)	5 (7.8)	11 (8.1)
Other	40 (20.0)	11 (17.2)	29 (21.3)

Note: WTC, World Trade Center; SD, standard deviation

* Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 2: Agreement of Risk Factor Measures, WTC-CARES and WTCHP (N=200)

	WTC-CARES	WTCHP	Agreement [a]
	n (%)	n (%)	Est. (95% CI)
Risk Behaviors			
Ever Cigarette Smoking, n (%)			
Overall	89 (44.5)	92 (46.0)	0.89 (0.83 , 0.95)
Prior to WTC exposure	88 (44.0)	90 (45.0)	0.90 (0.84 , 0.96)
During WTC exposure	34 (17.0)	42 (21.7)	0.85 (0.76 , 0.95)
After WTC exposure	44 (22.0)	44 (22.0)	0.85 (0.77 , 0.94)
Years of Cigarette Smoking, mean ± SD			
Overall	8.4 ± 12.2	10.1 ± 14.5	0.88 (0.84 , 0.91)
Prior to WTC exposure	7.1 ± 9.9	8.7 ± 11.7	0.91 (0.87 , 0.94)
During WTC exposure	0.6 ± 0.2	0.1 ± 0.2	0.50 (0.37 , 0.61)
After WTC exposure	1.4 ± 3.3	1.7 ± 3.9	0.84 (0.79 , 0.87)
Average Cigarette per Day, mean ± SD			
Prior to WTC exposure	4.7 ± 8.7	7.0 ± 10.6	0.61 (0.50 , 0.69)
During WTC exposure	2.3 ± 6.7	3.3 ± 7.9	0.57 (0.46 , 0.66)
After WTC exposure	2.0 ± 6.4	3.4 ± 8.0	0.73 (0.65 , 0.79)
Ever Alcohol Drinking, n (%)			
Overall	169 (84.5)	--	--
Prior to WTC exposure	167 (83.5)	--	--
During WTC exposure	152 (76.0)	--	--
After WTC exposure	154 (77.0)	143 (73.7)	0.51 (0.37 , 0.65)
Occupational Exposures [b]			
Prior to WTC Exposure			
Asbestos	65 (32.5)	89 (54.3)	0.18 (0.04 , 0.32)
Diesel/Gasoline Exhaust	99 (49.5)	107 (64.1)	0.18 (0.04 , 0.32)
Silica	49 (24.5)	58 (35.4)	0.24 (0.08 , 0.39)
Wood Dust	87 (43.5)	67 (41.0)	0.15 (0.00 , 0.30)
Fiber Glass	49 (24.5)	60 (36.4)	0.21 (0.05 , 0.36)
Industrial Cleaning Solution	52 (26.1)	61 (37.0)	0.12 (-0.03 , 0.27)
After WTC Exposure			
Asbestos	33 (16.5)	79 (48.5)	0.17 (0.05 , 0.29)
Diesel/Gasoline Exhaust	77 (38.5)	96 (57.8)	0.23 (0.10 , 0.37)
Silica	35 (17.6)	52 (31.7)	0.31 (0.16 , 0.47)
Wood Dust	58 (29.2)	63 (38.7)	0.16 (0.01 , 0.31)
Fiber Glass	29 (14.6)	54 (32.7)	0.10 (-0.04 , 0.25)
Industrial Cleaning Solution	34 (17.0)	53 (32.3)	0.14 (-0.02 , 0.29)

Note: WTC-CARES, World Trade Center Cancer Risk Epidemiology Study; WTCHP, World Trade Center Health Program; SD, standard deviation; CI, confidence interval; {N}, number of valid responses

[a] Agreement assessed by kappa (κ) statistic for categorical measures or intraclass correlation coefficient (ICC) for continuous measures

[b] For measures of occupational exposures, valid sample sizes for WTC-CARES range from 199 to 200; valid samples size for WTCHP range from 163 to 167

Table 3: Agreement by Case/Control Status, WTC-CARES and WTCHP (N=200)

	Agreement (95% CI) [a]			
Construct	Cases, n=64		Controls, n=136	
Ever Cigarette Smoking				
Overall	0.94	(0.85 , 1.00)	0.86	(0.78 , 0.95)
Prior to WTC exposure	0.94	(0.85 , 1.00)	0.88	(0.80 , 0.96)
During WTC exposure	0.88	(0.74 , 1.00)	0.83	(0.70 , 0.96)
After WTC exposure	0.85	(0.71 , 0.99)	0.85	(0.74 , 0.97)
Years of Cigarette Smoking				
Overall	0.89	(0.83 , 0.93)	0.87	(0.82 , 0.91)
Prior to WTC exposure	0.91	(0.84 , 0.95)	0.91	(0.87 , 0.94)
During WTC exposure	0.47	(0.23 , 0.65)	0.52	(0.38 , 0.64)
After WTC exposure	0.87	(0.79 , 0.92)	0.81	(0.75 , 0.86)
Average Cigarette per Day				
Prior to WTC exposure	0.80	(0.67 , 0.88)	0.55	(0.41 , 0.66)
During WTC exposure	0.60	(0.41 , 0.74)	0.55	(0.42 , 0.66)
After WTC exposure	0.56	(0.36 , 0.71)	0.82	(0.75 , 0.87)
Ever Alcohol Drinking				
After WTC exposure	0.52	(0.31 , 0.74)	0.49	(0.30 , 0.68)
Occupational Exposures				
Prior to WTC Exposure				
Asbestos	0.29	(0.03 , 0.55)	0.13	(-0.04 , 0.29)
Diesel/Gasoline Exhaust	-0.01	(-0.27 , 0.26)	0.25	(0.08 , 0.41)
Silica	0.17	(-0.12 , 0.45)	0.26	(0.08 , 0.44)
Wood Dust	0.14	(-0.12 , 0.40)	0.16	(-0.01 , 0.33)
Fiber Glass	0.07	(-0.21 , 0.35)	0.24	(0.06 , 0.42)
Industrial Cleaning Solution	0.10	(-0.16 , 0.37)	0.06	(-0.12 , 0.23)
After WTC Exposure				
Asbestos	0.32	(0.09 , 0.54)	0.12	(-0.02 , 0.26)
Diesel/Gasoline Exhaust	-0.02	(-0.36 , 0.15)	0.35	(0.19 , 0.50)
Silica	0.28	(-0.02 , 0.58)	0.31	(0.13 , 0.49)
Wood Dust	0.26	(0.00 , 0.53)	0.12	(-0.07 , 0.30)
Fiber Glass	0.10	(-0.21 , 0.41)	0.10	(-0.07 , 0.27)
Industrial Cleaning Solution	0.19	(-0.13 , 0.52)	0.07	(-0.10 , 0.25)

Note: WTC-CARES, World Trade Center Cancer Risk Epidemiology Study; WTCHP, World Trade Center Health Program; CI, confidence interval; Bold text denotes statistically different estimates, based on non-overlapping confidence intervals

[a] Agreement assessed by kappa (κ) statistic for categorical measures or intraclass correlation coefficient (ICC) for continuous measures

Table 4: Agreement by Enrollment Before vs. After Diagnosis, among Cases, WTC-CARES and WTCHP (N=64)

	Agreement (95% CI) [a]			
Construct	Enrolled Before Dx (n=36)		Enrolled After Dx (n=27)	
Risk Behaviors				
Ever Cigarette Smoking				
Overall	0.94	(0.83 , 1.00)	0.93	(0.78 , 1.00)
Prior to WTC exposure	0.94	(0.83 , 1.00)	0.93	(0.78 , 1.00)
During WTC exposure	0.93	(0.80 , 1.00)	0.79	(0.51 , 1.00)
After WTC exposure	0.87	(0.70 , 1.00)	0.82	(0.59 , 1.00)
Years of Cigarette Smoking				
Overall	0.85	(0.80 , 0.89)	0.91	(0.84 , 0.95)
Prior to WTC exposure	0.92	(0.88 , 0.94)	0.88	(0.79 , 0.93)
During WTC exposure	0.57	(0.45 , 0.67)	0.38	(0.12 , 0.59)
After WTC exposure	0.79	(0.72 , 0.84)	0.88	(0.80 , 0.93)
Average Cigarette per Day				
Prior to WTC exposure	0.54	(0.41 , 0.65)	0.78	(0.62 , 0.87)
During WTC exposure	0.54	(0.42 , 0.65)	0.62	(0.42 , 0.76)
After WTC exposure	0.77	(0.69 , 0.83)	0.63	(0.43 , 0.77)
Ever Alcohol Drinking				
After WTC exposure	0.69	(0.45 , 0.94)	0.21	(-0.17 , 0.60)
Occupational Exposures				
Prior to WTC Exposure				
Asbestos	0.45	(0.11 , 0.80)	0.07	(-0.29 , 0.44)
Diesel/Gasoline Exhaust	-0.05	(-0.42 , 0.31)	0.03	(-0.36 , 0.42)
Silica	-0.07	(-0.41 , 0.27)	0.42	(0.01 , 0.82)
Wood Dust	0.00	(-0.35 , 0.35)	0.28	(-0.12 , 0.68)
Fiber Glass	0.07	(-0.32 , 0.46)	0.05	(-0.35 , 0.45)
Industrial Cleaning Solution	0.08	(-0.24 , 0.39)	0.00	(0.00 , 0.00)
After WTC Exposure				
Asbestos	0.42	(0.10 , 0.74)	0.15	(-0.12 , 0.43)
Diesel/Gasoline Exhaust	0.00	(-0.34 , 0.34)	-0.26	(-0.60 , 0.08)
Silica	0.36	(-0.02 , 0.74)	0.18	(-0.27 , 0.63)
Wood Dust	0.34	(-0.01 , 0.70)	0.11	(-0.25 , 0.46)
Fiber Glass	0.17	(-0.27 , 0.60)	-0.08	(-0.21 , 0.05)

Note: WTC-CARES, World Trade Center Cancer Risk Epidemiology Study; WTCHP, World Trade Center Health Program; CI, confidence interval; Bold text denotes statistically different estimates, based on non-overlapping confidence intervals

[a] Agreement assessed by kappa statistic for categorical measures or intraclass correlation coefficient for continuous measures

Table 5: Agreement by Survey Mode, WTC-CARES and WTCHP (N=200)

	Agreement (95% CI) [a]			
Construct	Web (n=63)		Phone (n=137)	
Risk Behaviors				
Ever Cigarette Smoking				
Overall	0.94	(0.85 , 1.00)	0.87	(0.78 , 0.95)
Prior to WTC exposure	0.94	(0.85 , 1.00)	0.88	(0.80 , 0.96)
During WTC exposure	0.78	(0.58 , 0.98)	0.88	(0.78 , 0.98)
After WTC exposure	0.82	(0.64 , 0.99)	0.87	(0.77 , 0.97)
Years of Cigarette Smoking				
Overall	0.86	(0.77 , 0.91)	0.89	(0.84 , 0.92)
Prior to WTC exposure	0.87	(0.77 , 0.93)	0.93	(0.89 , 0.95)
During WTC exposure	0.33	(0.10 , 0.53)	0.56	(0.42 , 0.67)
After WTC exposure	0.79	(0.68 , 0.87)	0.86	(0.80 , 0.90)
Average Cigarette per Day				
Prior to WTC exposure	0.41	(0.19 , 0.60)	0.71	(0.60 , 0.79)
During WTC exposure	0.26	(0.02 , 0.47)	0.67	(0.56 , 0.75)
After WTC exposure	0.83	(0.73 , 0.89)	0.65	(0.54 , 0.74)
Ever Alcohol Drinking				
After WTC exposure	0.52	(0.23 , 0.81)	0.50	(0.34 , 0.66)

Note: WTC-CARES, World Trade Center Cancer Risk Epidemiology Study; WTCHP, World Trade Center Health Program; CI, confidence interval; Bold text denotes statistically different estimates, based on non-overlapping confidence intervals

[a] Agreement assessed by kappa statistic for categorical measures or intraclass correlation coefficient for continuous measures

Table 6: Agreement by Enrollment Before vs. After 1/1/2007, WTC-CARES and WTCHP (N=200)

	Agreement (95% CI) [a]			
Construct	Enrolled Before 2007 (n=95)		Enrolled in 2007 or later (n=105)	
Risk Behaviors				
Ever Cigarette Smoking				
Overall	0.85	(0.75 , 0.96)	0.92	(0.85 , 1.00)
Prior to WTC exposure	0.89	(0.80 , 0.98)	0.90	(0.82 , 0.99)
During WTC exposure	0.86	(0.72 , 0.99)	0.85	(0.72 , 0.98)
After WTC exposure	0.78	(0.63 , 0.94)	0.92	(0.83 , 1.00)
Years of Cigarette Smoking				
Overall	0.84	(0.76 , 0.89)	0.92	(0.88 , 0.94)
Prior to WTC exposure	0.91	(0.86 , 0.94)	0.91	(0.86 , 0.94)
During WTC exposure	0.59	(0.43 , 0.71)	0.43	(0.25 , 0.57)
After WTC exposure	0.75	(0.64 , 0.82)	0.90	(0.86 , 0.93)
Average Cigarette per Day				
Prior to WTC exposure	0.50	(0.33 , 0.64)	0.72	(0.60 , 0.81)
During WTC exposure	0.43	(0.25 , 0.58)	0.71	(0.60 , 0.80)
After WTC exposure	0.79	(0.69 , 0.86)	0.65	(0.52 , 0.75)
Ever Alcohol Drinking				
After WTC exposure	0.49	(0.27 , 0.70)	0.53	(0.34 , 0.71)

Note: WTC-CARES, World Trade Center Cancer Risk Epidemiology Study; WTCHP, World Trade Center Health Program; CI, confidence interval; Bold text denotes statistically different estimates, based on non-overlapping confidence intervals

[a] Agreement assessed by kappa statistic for categorical measures or intraclass correlation coefficient for continuous measures

Table 7: WTCHP measures of behavioral risk factors, by WTC-CARES enrollment status (N=102)

Construct	Enrolled (n=64) n (%)	Did not Enroll (n=38) n (%)	p-value [a]
Risk Behaviors			
Ever Cigarette Smoking			
Overall	33 (51.6)	18 (50.0)	0.8807
Prior to WTC exposure	33 (51.6)	18 (50.0)	0.8807
During WTC exposure	18 (28.6)	13 (36.1)	0.4365
After WTC exposure	15 (23.4)	12 (33.3)	0.2847
Years of Cigarette Smoking, mean ± SD			
Overall	11.1 ± 13.9	13.5 ± 16.2	0.4303
Prior to WTC exposure	10.1 ± 11.8	11.4 ± 14.2	0.6445
During WTC exposure	0.1 ± 0.2	0.2 ± 0.3	0.2530
After WTC exposure	1.5 ± 3.6	2.1 ± 4.3	0.4469
Average Cigarette per Day, mean ± SD			
Prior to WTC exposure	7.5 ± 9.6	7.2 ± 10.3	0.9005
During WTC exposure	4.4 ± 8.4	5.1 ± 9.0	0.7011
After WTC exposure	3.0 ± 7.2	4.9 ± 9.0	0.2385
Ever Alcohol Drinking			
After WTC exposure	38 (61.3)	22 (62.9)	0.8787

Note: WTCHP, World Trade Center Health Program; SD, standard deviation
[a] 2-sided chi-square test for comparison of categorical measures, t-test for comparison of continuous measures

REFERENCES

1. Landrigan PJ, Lioy PJ, Thurston G, et al. Health and environmental consequences of the world trade center disaster. *Environ Health Perspect.* 2004;112(6):731-739.
2. Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives.* 2002;110(7):703-714.
3. Pleil JD, Vette AF, Johnson BA, Rappaport SM. Air levels of carcinogenic polycyclic aromatic hydrocarbons after the World Trade Center disaster. *Proc Natl Acad Sci U S A.* 2004;101(32):11685-11688.
4. Li JH, Cone JE, Kahn AR, et al. Association Between World Trade Center Exposure and Excess Cancer Risk. *JAMA.* 2012;308(23):2479-2488.
5. Solan S, Wallenstein S, Shapiro M, et al. Cancer incidence in world trade center rescue and recovery workers, 2001-2008. *Environ Health Perspect.* 2013;121(6):699-704.
6. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. *N Engl J Med.* 2007;356:1944-1956.
7. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9(1):e86023.
8. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol.* 2010;39(1):166-181.
9. Berthiller J, Straif K, Agudo A, et al. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-845.
10. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48(11):3282-3287.
11. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst.* 2007;99(10):777-789.
12. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part B: Biological Agents.* Vol 100B; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part E: Personal habits and indoor combustions.* Vol 100E; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
14. Dasaro CR, Holden WL, Berman KD, et al. Cohort Profile: World Trade Center Health Program General Responder Cohort. *Int J Epidemiol.* 2017;46(2):e9.

15. National Center for Health Statistics. National Health Interview Survey, 2015. Public-use data file and documentation. 2016; https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.
16. CDC (Centers for Disease Control and Prevention). 2016 Behavioral Risk Factor Surveillance System Questionnaire. 2015; https://www.cdc.gov/brfss/questionnaires/index.htm.
17. National Cancer Institute. Tobacco Use Supplement to the Current Population Survey. 2015; https://cancercontrol.cancer.gov/brp/tcrb/tus-cps/info.html.
18. Kelsey K. CoHANDS Study Questionnaire. In:2017.
19. Olshan AF. CHANCE Questionnaire. In: Manderski M, ed2017.
20. Collins D. Pretesting survey instruments: an overview of cognitive methods. *Qual Life Res.* 2003;12(3):229-238.
21. Caspar RA, Lessler JT, Willis GB. Cognitive Interviewing A “How-To” Guide. *Meeting of the American Statistical Association* 1999; http://appliedresearch.cancer.govareascognitiveinterview.pdf. Accessed 1/5/2017.
22. J. SM, Willis J. Application of cognitive interviewing to improve self-administered questionnaires used in small scale social pharmacy research. *Research in Social & Administrative Pharmacy.* 2014;10:469-474.
23. Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement.* 1960;XX(1):37-46.
24. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics.* 1977;33(1):159-174.
25. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med.* 2016;15(2):155-163.
26. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-428.
27. Coughlin SS. Recall bias in epidemiology studies. *J Clin Epidemiol.* 1990;43(1):87-91.
28. Szklo M, Nieto FJ. *Epidemiology : beyond the basics.* 3rd ed. Burlington, Mass.: Jones & Bartlett Learning; 2014.

RISK FACTORS FOR HEAD AND NECK CANCER IN A COHORT OF WORLD TRADE CENTER RESPONDERS: A NESTED CASE-CONTROL STUDY

By

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Manuscript 2 of 3 of a dissertation entitled

MEASUREMENT AND EVALUATION OF RISK FACTORS FOR CANCERS OF THE HEAD AND NECK IN A COHORT OF 9/11 WORLD TRADE CENTER RESPONDERS

Submitted to the

School of Public Health

And the

Graduate School – New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Written under the direction of

Judith M. Graber, PhD, MS

ABSTRACT

Background: Head and neck cancers (HNCs) may be among the health consequences of involvement in the World Trade Center (WTC) response efforts that followed September 11, 2001. We conducted a nested case-control study of WTC Health Program (WTCHP) General Responders to examine the effects of WTC exposures and behavioral risk factors on HNC.

Methods: We enrolled 64 cases and 136 controls without cancer, matched on age, sex, and race/ethnicity within risk sets. We assessed behavioral risk factors (tobacco, alcohol, sexual activity) during three time periods (prior to, during, and after WTC exposure until case diagnosis) via questionnaire. We obtained WTC exposure information (duration [first to last day], total days, and location of work) via a data request from the WTCHP General Responder Data Center. We estimated odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression and assessed interaction among exposures.

Results: Responders in protective services occupations had increased odds (OR: 2.51, 95% CI: 1.09, 5.82) of HNC compared to those in other occupations. Among those in non-protective services occupations, arriving to the WTC effort on 9/11/01 as opposed to later was also significantly associated with HNC (OR: 3.77; 95% CI: 1.00, 14.11). Duration of work was not significantly associated with HNC. Lifetime and post-WTC years of cigarette smoking and post-WTC number of sex partners were positively and significantly associated with HNC, while alcohol consumption was not.

Discussion: Among WTCHP general responders, increased cigarette smoking, post-WTC number of sex partners, and having a protective services occupation are associated with

increased HNC risk. These findings suggest opportunities for risk factor mitigation (e.g., smoking cessation, human papillomavirus vaccination) and contribute to a risk factor profile which may assist WTCHP clinicians with identifying high-risk responders and improve detection and treatment outcomes in this population.

INTRODUCTION

The collapse of the World Trade Center (WTC) buildings on September 11, 2001 (9/11) resulted in unprecedented local pollution that persisted for several months. Those involved in the WTC response efforts (i.e., rescue, recovery, and cleanup) were possibly exposed to multiple known and suspected human carcinogens, including asbestos, silica, benzene, polychlorinated biphenyls, polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), and a variety of dusts and metals.[1-3] Because these substances were inhaled, particularly via mouth breathing,[4] cancers of the head, neck, and upper respiratory tract are plausible health consequences of WTC-related exposures. A 40% excess incidence (standardized incidence ratio [SIR], 1.4 [95% CI, 1.01-1.89]) of head and neck cancers (HNC) diagnosed between 2009 and 2012 among World Trade Center Health Program (WTC) General Responder Cohort (GRC) members has been observed, suggesting that these cancers may be among the health consequences of exposure to the dust and debris.[5] Other studies have reported excess incidence of all and other specific cancer sites, including prostate and thyroid, among WTC-exposed populations. [6,7]

Several risk factors are associated with HNC in the general population, including tobacco smoking, heavy alcohol consumption, exposure to asbestos and wood, cement, and metal dusts, and, for oropharyngeal cancers, persistent oral infection with oncogenic types of the human papillomavirus (HPV), usually HPV-16.[8-16] In addition, interaction among occupational and behavioral risk factors in the risk of HNC has been documented[17-19] As well, among WTC responders, risk behaviors may have changed during or after the WTC response (e.g., increased alcohol consumption, relapse to smoking). Therefore, the possible effects of WTC exposures on HNC risk may be direct, mediated, or moderated, warranting careful consideration of WTC exposures in the context of other risk factors.

To assess the role of WTC exposure and behavioral risk factors in HNC risk, we conducted a case-control study nested within the WTCHP GRC, hypothesizing that HNC occurrence is positively associated with intensity and duration of WTC exposure, tobacco smoking, alcohol consumption, and sexual activity (a well-established indicator of HPV infection risk[14,20,21]).

METHODS

Study Population

All study participants were WTCHP GRC members. The GRC is one of the longitudinal cohorts formed following 9/11 supported by the Centers for Disease Control and Prevention (CDC), National Institute of Occupational Safety and Health (NIOSH) WTCHP. The GRC includes responders (other than New York City Fire Department [FDNY] responders, followed separately) who participated in the WTC response efforts between September 11, 2001 and July 31, 2002. Details about eligibility and benefits are published elsewhere.[22] Briefly, to be eligible for WTCHP GRC membership, responders must have worked or volunteered for at least four hours between September 11 through 14, 2001, at least 24 hours during the month of September 2001, or at least 80 hours between October 2001 and July 2002; or handled or processed human remains in the office of the chief medical examiner; or worked for at least 24 hours cleaning tunnels for the Port Authority Trans-Hudson Corporation (PATH). GRC members receive an initial physical examination and are eligible for annual health monitoring visits thereafter, as well as treatment visits for WTC-certified conditions. Monitoring visits include clinical examination as well as at-home completion of questionnaires that a nurse or physician reviews during the clinical visit. The WTC General Responder Data Center (GRDC) in the Icahn School of Medicine at Mount Sinai in New York City maintains data collected from consented GRC members during WTCHP GRC enrollment and follow-up, including WTC-related exposure, clinical, and questionnaire data.

Case and Control Selection

We selected study participants among living GRC members who had previously consented to contact about participation in WTC-related research studies. Eligible cases had HNC diagnosed between 2002 and 2016 (International Classification of Disease [ICD]-9 codes 140-149.9, 160-161.0; ICD-10 codes C00.0-C14.9, C32-C32.9). We identified 94 eligible cases, of whom 64 (68.1%) consented to participate. For each enrolled case, we identified GRC members without a cancer diagnosis as potential controls using risk-set sampling, with risk sets defined as GRC members who were in the cohort at the time of case diagnosis and who had not yet attained the case's age at diagnosis. This method of selecting controls (from each case's person-time at risk) allows for calculation of odds ratios that are robust estimates of rate ratios.[23] Potential controls were matched on age, sex (male vs. female), and race (non-Hispanic white vs. other) within risk sets, given that HNC incidence is known to be more than twice as high among men than women and among non-Hispanic whites than non-whites.[24] One hundred thirty-six (136) controls (at least two per case) enrolled in the study.

Questionnaire Development

To inform questionnaire development, we reviewed standardized surveillance instruments (e.g., National Health Interview Survey [NHIS][25] and the Behavioral Risk Factor Surveillance System [BRFSS][26]) as well as questionnaires from other retrospective studies of HNC risk factors.[27,28] An expert panel including WTCHP GRC clinicians, a survey methodologist, a tobacco dependence specialist, oncologists, and cancer epidemiologists reviewed the questionnaire to assess face and content validity, as well as cultural appropriateness. We then evaluated the revised draft using cognitive interviewing procedures in a convenience sample of nine GRC members and three non-WTC exposed persons with a history of cancer. (Cognitive interviewing is a technique used to study the process through which a respondent interprets a question and formulates a response[29]).

The final study questionnaire included domains that assess the major population risk factors for HNC: tobacco use, alcohol use, marijuana use, sexual activity, and exposure to environmental toxicants during each of three time periods: (1) before September 11th 2001, (2) during the time that the participant was involved in the WTC response efforts (except for environmental exposures, which were previously collected by the GRDC), and (3) subsequently until the time of HNC diagnosis (for the matched case).

Recruitment and Data Collection

Recruitment commenced in July 2017, and data collection continued until April 2018. Prospective participants received mailed letters inviting them to participate in the study, dubbed the World Trade Center Cancer Risk Epidemiology Study (WTC-CARES).

The letter included information about the study, as well as a telephone number and web address where respondents could choose to schedule their telephone interview, elect to complete the survey online (offered because common sequelae of HNC include difficulty speaking), or opt out of participation. Specially-trained study interviewers then attempted to contact potential participants and administer the questionnaire via telephone.

WTC Exposure Measures

We obtained deidentified WTC exposure information for study participants via a data request to the WTCHP GRDC. This included multiple dimensions of WTC-related exposure, including date of arrival, primary duty, duration of exposure, and total number of days exposed. We defined date of arrival as a responder's first day of work on the WTC effort and categorized participants into three groups: 1) arrived on 9/11/01, 2) arrived on 9/12/01 or 9/13/01, or 3) arrived on or after 9/14/01. We defined duration of exposure as the difference, in days, between first and last days of work on the WTC effort and total days of exposure as the number of days the responder actually worked on the WTC effort. The WTCHP assessed primary work location (i.e., on the pile/in the pit, adjacent to the pile/pit, landfill, barges/loading piers, or elsewhere) during September 2001, October 2001, November through December 2001, and January through June 2002. We further categorized work location using a tiered approach, such that those who spent the majority of at least one time period "on the pile/in the pit" were classified as 'on the pile'; those who did not work on the pile but spent time "adjacent to the pile/pit" were classified as 'adjacent to the pile'; and those who did not work on or adjacent to the pile were classified as 'elsewhere.'

Behavioral and Occupational Risk Factor Measures

We assessed behavioral risk factors, including years of tobacco smoking, cumulative alcohol exposure, and number of sex partners, for the three study periods (before, during, and after WTC exposure). We selected years of tobacco smoking to estimate tobacco exposure, because increased HNC risk has been observed for long-term infrequent smokers[8] and because duration, separate from intensity, of smoking has been linked to smoking-related health risks in general.[30,31] We then estimated lifetime years of cigarette smoking as the sum of smoking years during each of the three time periods.

We quantified average alcohol consumption during each study time period as the product of usual quantity per drinking occasion and usual frequency, converted to drinks per week (as described by Friesema and colleagues[32]). Since duration of study time periods varied by participant, we then multiplied this quantity-frequency measure by the total reported years of drinking during each respective study period to estimate cumulative alcohol consumption as a function of both average consumption and duration of consumption. We estimated lifetime cumulative alcohol consumption by summing across all three time periods.

We assessed lifetime and period-specific number of sex partners, a well-established surrogate for human papillomavirus infection (HPV) and a documented risk factor for certain HNCs[14,20,21], using multiple-choice questions: *In your entire life/Before nine-eleven/Between first and last days of WTC work/Between last day of WTC work and [case diagnosis month/year], how many different sexual partners have you had? Please count every partner, even those you were with only once. By 'sex' we mean sexual* *intercourse, oral sex, or anal sex.* with response options: *0 partners, 1 partner, 2 to 5 partners, 6 to 10 partners, 11 to 15 partners, 16 to 25 partners, 26 to 50 partners, 51 to 100 partners, or more than 100 partners*. Based on the distribution among cases, we classified participants into two groups for each of the study time periods: 6 or more partners vs. fewer than 6 partners.

Given that occupation was related to WTC effort job functions[33] and that prior research has documented elevated HNC risk among certain occupational groups,[34-37] we collected data on primary occupation outside the WTC response efforts via the study survey. GRC member occupations generally fall into the following groups: (1) protective services (i.e., law enforcement, firefighter, emergency services, military); (2) construction; (3) electrical, telecommunications, and other installation and repair; (4) transportation and material movers; (5) business, engineering, and administration; and (6) other.[33] Based on case distribution of occupation groups, we classified participants into two groups for analysis: protective services vs. other. We also assessed occupational exposures before and after the WTC response to environmental toxicants such as asbestos and dusts as ever/never, frequency (days per week, month or year), and duration (number of days, weeks, months, or years) of exposure.

Protection of Human Subjects

The Health Sciences Institutional Review Board at Rutgers University reviewed and approved the study protocol, including recruitment, consent, and data collection procedures (Pro20160001045). This included details of an Honest Broker agreement, whereby a designated entity maintained all protected health information (PHI) for WTC-

CARES. We received only deidentified survey data that included a unique ID number, and the WTCHP data we obtained from the GRDC included the same ID number. We then merged the two data sources by this variable. The Honest Broker agreement was also outlined in our Data Use Agreement (DUA) between Rutgers University and the GRDC. We additionally obtained a certificate of confidentiality from the CDC.

Statistical Analysis

We used conditional logistic regression to estimate the association between our explanatory variables and occurrence of HNC, accounting for the nested and matched design. Based on distribution among cases and model fit, we modeled primary work location as on the pile/pit vs. elsewhere and date of arrival as on 9/11 vs. later. We assessed the impact of variable inclusion and functional form by comparing -2 log likelihood statistics between full and nested models. For standardized interpretation of continuous risk behavior variables (i.e., tobacco smoking and alcohol consumption) in the context of study time periods of varying duration, we estimated the effects associated with an increase of 1 standard deviation (SD), based on the distribution among cases. We assessed interaction between work location and duration of exposure and between date of arrival and occupation by including respective cross-product term in the models, and examined stratified effect estimates when interaction was suggested by a p-value less than 0.2.

When multiple measures of a construct were available (e.g., pack-years of smoking vs. years of smoking), we performed sensitivity analyses to assess whether including an alternate measure for that construct would impact results or improve model fit, as indicated by a smaller Akaike information criterion (AIC). Additional sensitivity analyses included a comparison of cases enrolled relative to those identified but not enrolled in the present study, using chi-square and t tests for categorical and continuous variables, respectively. Additionally, we repeated our primary regression analyses restricted to cases diagnosed during 2005 or later to assess the impact of including cases diagnosed shortly after 9/11.

All statistical tests were two-sided, with p-values less than 0.05 considered indicative of statistical significance. We performed all analyses using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Participant Characteristics

As expected from the matched design, case and control groups were similar with respect to age and sex distribution; however, the control group was notably more racially diverse (34.6% non-white or Hispanic vs. 17.2% of cases; Table 1), suggesting an imperfect match on race/ethnicity, so we adjusted for race/ethnicity in multivariable analyses. Among cases, the most commonly diagnosed HNC was oropharyngeal cancer (43.8%, including base of tongue, tonsil, and other oropharynx); 60.9% were employed in protective services occupations and 25.0% had ever served in the military; nearly half (49.2%) started on the WTC effort on 9/11, and 41.3% worked on the pile. Among controls, 46.3% were employed in protective services occupations and 16.2% had served in the military; the majority (61.6%) started on the WTC effort after 9/11, and 37.7%

worked on the pile. Mean total days of work was similar for cases and controls, but mean duration of work was somewhat longer for controls (117.9 vs. 132.0 days).

During each of the study time periods (lifetime and before, during, and after WTC exposure until case diagnosis), both ever smoking prevalence and mean years of smoking were higher for cases (Table 2). However, indicators of alcohol use (prevalence and cumulative consumption) were higher for controls. Prevalence of having six or more sex partners was higher for controls during the pre- and during-WTC exposure time periods but was higher for cases during the post-WTC period.

Both mean duration of work and mean total days of work were lowest for those who worked on the pile/in the pit and increased with distance from the WTC pile/pit (Table 3). This relationship was similar for cases and controls (data not shown).

Regression Models

Table 4 presents the main effects of WTC exposures and risk behaviors over the lifetime (Model 1), pre-9/11 (Model 2), during WTC exposure (Model 3), and after WTC exposure (Model 4). Having a protective services occupation was significantly associated with a 2.5-fold increase in odds of HNC (OR: 2.51, 95% CI: 1.09, 5.82), adjusted for WTC exposure measures and lifetime risk behaviors; this association was similar when assessing effects from each study time period. HNC was not significantly associated with arrival date, duration of WTC work, or work location in any model.

Years of cigarette smoking was positively associated with HNC in all models, with the strongest associations observed when considering lifetime and post-WTC exposure smoking. For example, an increase of 1 SD (per case distribution, as per Table

2) lifetime years of smoking was associated with a 78% increase in odds of HNC (OR: 1.78, 95% CI: 1.04, 3.03). Cumulative alcohol consumption was not significantly associated with HNC in any model. Lifetime number of sex partners was not significantly associated with HNC; however, having six or more (vs. fewer than six) sex partners during the post-WTC exposure period was associated with a nearly three-fold increase in odds of HNC (OR: 2.92, 95% CI: 1.15, 7.46).

Results suggested that occupation may moderate the effect of arrival date (p for interaction = 0.1616, Table 5). Among those not in protective services occupations, arriving on 9/11 as opposed to later was associated with 3.77-fold increased odds (OR: 3.77, 95% CI: 1.00, 14.11) of HNC, adjusted for other WTC exposure measures and lifetime risk behaviors, as compared to the null association between arrival date and HNC among those in protective services (OR: 1.18, 95% CI: 0.42, 3.33). These findings were similar across all four models. In addition, we observed interaction between work location and duration of work, such that duration was inversely associated with HNC, only among those who did not work on the pile (p for interaction=0.0422). Among those who did not work on the pile/pit, each 30-day increase in work duration was associated with an 18% decrease in odds of HNC (OR: 0.82, 95% CI: 0.69, 0.98), adjusted for other WTC exposures, occupation, and lifetime risk behaviors, whereas this association was null among those who did work on the pile/pit (OR: 1.06, 95% CI: 0.89, 1.26).

Sensitivity Analyses

Substituting pack-years of smoking (i.e., years of smoking times average number of packs per day) in place of years of smoking in the main effect models (Table 4) did not substantively change the observed effects of WTC exposure or improve model fit; lifetime pack-years of smoking was positively associated with increased odds of HNC (OR: 1.79 per 1 SD increase, 95% CI: 1.07, 3.00), but pre-, during-, and post-WTC exposure pack-years of smoking were not significantly associated with HNC (Table 6). Substituting alternate measures of cumulative alcohol consumption, including years of drinking and total number of binge drinking days, yielded similar results to those presented in Table 4 (Tables 7 and 8). Addition of survey mode to the models did not substantively change the regression results, and survey mode was not significantly associated with HNC in any model (Table 9).

Comparing cases enrolled (n=64) to those identified but not enrolled (i.e., those who were deceased, refused participation, or could not be reached; n=38; Table 10), study participants were somewhat younger on 9/11 than non-participants (mean: 41.9 vs. 45.9 years, p=0.0419) and were more likely to be female (10.9% vs. 0%, p=0.0346). However, participants and non-participants did not significantly differ with respect to race/ethnicity (% non-Hispanic white: 82.8% vs. 83.8%, p=0.9000), mean duration of work (117.9 vs. 133.7, p=0.4627), mean total days of work (72.7 vs. 59.3, p=0.3721), arrival date (% arriving on 9/11: 49.2% vs. 37.8%, p=0.2699), or work location (% on the pile: 41.3% vs. 35.1%, p=0.5437).

Regression analyses excluding cases diagnosed prior to 2005 (n=4) yielded results similar to those reported in Table 4 (data not shown).

DISCUSSION

In response to a reported excess of HNC incidence among WTC general responders,[5] we conducted a nested case-control study to identify risk factors for HNC in this population, including WTC exposures and risk behaviors before, during, and after involvement in the WTC response. We observed that employment in protective services occupations, increased lifetime and post-WTC years of cigarette smoking, and having six or more sex partners during the post-WTC period were significantly associated with increased risk for HNC. Additionally, arrival on 9/11 as opposed to later was strongly associated with increased risk of HNC among those not in the protective services; however, contrary to our hypotheses, neither work location nor duration of work were positively associated with HNC as main effects.

Employment in the protective services was strongly associated with increased risk of HNC; however, epidemiologic or mechanistic support for this observation outside this population is lacking. Thus, this association may be more likely reflective of risk associated with job tasks specific to those in the protective services during the WTC efforts (e.g., search and rescue[33]) or lifestyle factors associated with these occupations, rather than risks associated with these occupations in general.

The observation that arriving on 9/11 as opposed to later was associated with increased estimated risk of HNC only among those not employed in protective service occupations was surprising. A study of asthma outcomes among WTC-exposed persons reported that protective services workers were less likely than construction and public agency workers to have worn a mask or respirator on 9/11;[33] as such, differential use of personal protective equipment (PPE) may not explain this observation, but may contribute to the overall risk observed for workers in the protective services. Other potential explanations for consideration include variation in tasks by occupation and phase of the WTC effort, other occupational exposures before and after the WTC response, and misclassification of arrival date.

For those who worked on the pile, duration of work was not associated with HNC risk; however, duration was inversely associated with HNC for those who worked elsewhere on the WTC effort. This finding could suggest a protective effect of longer work duration, provided the work was not on the pile; however, it is more likely indicative of differing job tasks and exposures by location and phase of the WTC response. Moreover, it may suggest that the nonsignificant inverse association observed between duration and HNC risk overall may be driven by lower risk among those who did not work on the pile.

Years of tobacco smoking was significantly and positively associated with HNC, particularly when considering the post-WTC exposure period. This finding is consistent with existing literature linking tobacco smoking to HNC and adds to the growing body of research implicating the importance of smoking duration in risk of HNC.[8,38] In contrast, we did not observe a significant effect of smoking pack-years (years of smoking times average packs per day) during the post-WTC study period, which suggests that smoking even at lower levels following the WTC response carries elevated risk for HNC in this population. Previous studies have identified a positive association between post-traumatic stress disorder (PTSD) and smoking outcomes among WTCHP members.[39,40] Thus the observed effect of post-WTC smoking duration may reflect continued or relapse to smoking following the WTC response period, potentially mediated by PTSD. Taken together, targeted smoking cessation interventions for WTCHP responders may be important for mitigating risk for HNC, especially for those who suffer from PTSD.

Number of sex partners in the post-WTC period was significantly associated with increased odds of HNC. Prior research has found strong associations between increased sexual activity and both HPV infection and oropharyngeal cancer.[14,21,41-44] HPV-associated HNC tumors are typically cancers of the oropharynx,[45,46] which were the most common type of HNC among cases in this study. Therefore, oral HPV infection, possibly related to increased sexual activity following the WTC response, may contribute to HNC risk in WTC responders, suggesting that HPV-prevention measures (e.g., risk reduction education, vaccination) may benefit this population. In October of 2018, the U.S. Food and Drug Administration (FDA) expanded the approved use of Gardasil 9 (a 9-valiant recombinant HPV vaccine) to include women and men through age 45.[47] Since HPV vaccination has been shown to reduce vaccine-type oral HPV infection,[48] our findings suggest that HPV vaccination should be encouraged among WTC-exposed persons as indicated by age.

Although heavy alcohol consumption is a strong population risk factor for HNC,[11] we did not observe a significant negative association between cumulative alcohol consumption and HNC. This was surprising and may be indicative of under-reporting of drinking behaviors among cases, heavier drinking among GRC members relative to the general population, or the presence of unmeasured alcohol-related comorbidities among study participants. An additional consideration is that cancers of the oropharynx attributed to HPV infection do not tend to be associated with tobacco or alcohol and appear to be etiologically distinct from other types of HNC.[49] As such, it is possible that the lack of association with alcohol consumption reflects the presence of multiple heterogeneous causal pathways for HNC in this population.

This study is subject to several limitations. Despite the efficient nested matched design, the small sample size yielded imprecise estimates, suggesting that even null findings may be the result of inadequate power. Sample size also did not permit cancer site-specific analyses, which may have limited our ability to identify effects of exposures that are typically associated with certain HNC subtypes. For example, tobacco and alcohol consumption are strong population risk factors for oral-nasal and laryngeal cancers, whereas oropharyngeal cancers are typically associated with HPV infection.[14] As such, the lack of positive, significant associations observed for lifetime number of sex partners and alcohol consumption may reflect cancer heterogeneity among cases. It is therefore conceivable that specific WTC-related exposures may be associated with only certain types of HNC. As additional cases emerge in this population, future study may provide adequate power to perform site-specific analyses that can shed light on these questions.

Offering a web-based option for participation may have introduced a mode effect;[50] however, offering a non-verbal option was critical, given that common sequelae of HNC include impeded speech, and substantial care was taken to maximize similarities between survey modes. For example, the interviewer- and self-administered surveys were identical with respect to text and supplemental information, and the interviewers were specially trained to avoid script deviations. Although sensitivity analyses found no significant association between survey mode and HNC, further exploration into the potential impact of mode may be warranted.

Our analyses included four cases diagnosed between 2002 and 2005 with the hypothesis that high intensity exposures may have promoted or accelerated early carcinogenic processes that otherwise might not have progressed. However, cancers among GRC members must be diagnosed after September 2005 in order to be certified as "WTC-related" by NIOSH.[51] The contrast between our case definition and the WTCHP certification requirements may raise concerns regarding disease latency; however, since sensitivity analyses excluding these four pre-2005 cases yielded similar results to those presented in Table 4, their inclusion in study analyses should not detract from our results.

Our findings should be considered in light of potential biases, including self-selection into the WTCHP GRC, selection into this study, survivorship, measurement error, and possible comorbidities not accounted for in analysis. Given that WTCHP GRC members are self-selected, it is possible that responders who have not joined the WTCHP have different risk factor profiles than those who are members and eligible for the present study. Results may also be subject to the healthy worker survivor effect (HWSE), given that participants were members of a working population, although this would likely result in underestimation of true effect. HWSE may also explain why duration of work was inversely associated with proximity to the WTC pile; for example, responders who had physical difficulty working on the pile may have left after a relatively short period of time. Our selection and enrollment procedures may also have introduced bias, if those who were eligible and consented to participation in our study differed from those who did not. However, there were no differences in WTC exposure measures when comparing cases who enrolled to those who did not enroll in this study, suggesting that the impact of response bias is minimal. Finally, since both WTC-related and behavioral exposures were self-reported, misclassification is possible; however comprehensive survey development and cognitive testing of the instrument may have lessened the potential for differential recall.

A diagnosis of HNC can be devastating, particularly for WTC responders, many of whom endure PTSD as a result of their experience.[52] Risk of treatment failure and death is high, with five-year survival rates of 62% for cancers of the oral cavity and pharynx and 60% for laryngeal cancers.[53] Many patients that do survive suffer from persistent symptoms even after treatment, including disfigurement, difficulty swallowing, sleep disturbances, pain, depression, and anxiety.[54] There is no effective screening for HNC; however, our results contribute to development of a risk factor profile for WTC responders that can assist WTCHP clinicians with identifying high-risk responders, which may in turn improve detection and treatment outcomes in this population.

Table 1: Characteristics of Cases and Controls, WTC Cancer Risk Epidemiology Study

Characteristic	Cases (n=64)	Controls (n=136)
Demographics		
Age on 9/11, mean ± SD	41.9 ± 6.8	41.6 ± 6.8
Age at enrollment in WTCHP, mean ± SD	51.1 ± 9.1	46.8 ± 7.5
Male sex, n (%)	57 (89.1)	120 (88.2)
Non-Hispanic white, n (%)	53 (82.8)	89 (65.4)
Primary Occupation, n (%)		
Protective Services	39 (60.9)	63 (46.3)
Construction, Cleanup, Machines	9 (14.1)	33 (24.3)
Communications Technicians, Other	16 (25.0)	40 (29.4)
Ever Served in Military, n (%)	16 (25.0)	22 (16.2)
WTC Exposure Measures		
Date of Arrival on Site, n (%)		
9/11	31 (49.2)	51 (38.4)
9/12 - 9/13	18 (28.6)	45 (33.8)
9/14 or later	14 (22.2)	37 (27.8)
Work Location, n (%)		
On the pile/in the pit	26 (41.3)	49 (37.7)
Adjacent to pile/pit	25 (39.7)	60 (46.2)
Elsewhere	12 (19.1)	21 (16.2)
Duration of WTC Work (first to last day), mean ± SD	117.9 ± 101.8	132.0 ± 104.9
Total Days Worked/Volunteered, mean ± SD	72.7 ± 77.5	72.6 ± 69.5
Risk Behaviors		
Smoking Status, n (%)		
Current	5 (7.8)	10 (7.4)
Former	28 (43.8)	46 (33.8)
Alcohol Consumption, n (%)		
Current	36 (56.3)	102 (75.0)
Former	14 (21.9)	17 (12.5)
Age at sexual debut, mean ± SD	17.4 ± 2.6	16.6 ± 2.9
Number of lifetime sex partners, n (%)		
1 to 5	24 (37.5)	36 (26.5)
6 to 10	18 (29.5)	37 (29.8)
11 or more	19 (31.2)	51 (41.1)
Ever diagnosed with a sexually transmitted infection, n (%)	6 (9.4)	17 (12.6)
Cancer Information (cases only)		
Age at diagnosis, mean ± SD	51.8 ± 8.1	
Cancer Site, n (%)		
Larynx	11 (17.2)	
Oral Cavity [a]	13 (20.3)	
Oropharynx [b]	28 (43.8)	
Other [c]	12 (18.8)	

Note: WTC, World Trade Center; SD, standard deviation; Counts may not sum to group total due to item nonresponse

[a] Oral cavity includes tongue (c02), gum (c03), palate (c05), other oral cavity and pharynx (c14)

[b] Oropharynx includes base of tongue (c01), tonsil (c09), oropharynx (c10)

[c] Other includes nasopharynx (c11), nasal cavity and middle ear (c30), accessory sinuses (c31), parotid gland (c07), other major salivary glands (c08)

Table 2: Lifetime and Pre-, During-, and Post- WTC Exposure Behavioral Risk Factors among Cases and Controls, WTC Cancer Risk Epidemiology Study

Risk Factor	Study Group [a]	Lifetime, until case diagnosis	Prior to WTC exposure	During WTC exposure	After WTC exposure, until case diagnosis
Ever Cigarette Smoking, n (%)	Cases	33 (51.6)	33 (51.6)	16 (25.0)	19 (29.7)
	Controls	56 (41.2)	55 (40.4)	18 (13.2)	25 (18.4)
Years of Cigarette Smoking, mean ± SD	Cases	10.5 ± 12.7	8.5 ± 9.9	0.1 ± 0.2	1.9 ± 3.8
	Controls	7.5 ± 11.9	6.4 ± 9.9	0.0 ± 0.2	1.1 ± 3.1
Ever Alcohol Consumption, n (%)	Cases	50 (78.1)	50 (78.1)	44 (68.8)	44 (68.8)
	Controls	119 (87.5)	117 (86.0)	108 (79.4)	110 (80.9)
Cumulative Alcohol Consumption, [b] mean ± SD	Cases	149.4 ± 288.0	110.3 ± 212.2	1.3 ± 3.2	39.5 ± 98.6
	Controls	171.5 ± 267.0	119.4 ± 202.9	1.5 ± 3.8	52.4 ± 97.6
6+ Sex Partners, n (%)	Cases	37 (60.7)	32 (52.5)	[c]	15 (24.6)
	Controls	88 (71.0)	74 (59.2)	9 (7.1)	13 (10.2)

Note: WTC, World Trade Center; SD, standard deviation
[a] Cases, n=64; Controls, n=136
[b] Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption)
[c] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 3: Average Duration of Work and Total Days of Work by Work Location, WTC Cancer Risk Epidemiology Study

	Mean ± SD	
Work/Volunteer Location	Duration of WTC Work, Days [a]	Total Days of WTC Work [b]
On Pile	118.6 ± 96.8	64.5 ± 64.9
Adjacent to Pile	130.5 ± 107.5	76.2 ± 73.1
Elsewhere	139.8 ± 108.3	85.2 ± 84.7

Note: SD, standard deviation
[a] Duration defined as number of days between first and last day on site
[b] Total days was defined as the actual number of days on site, excluding days not on site

Table 4: Multivariable Associations of WTC-related Exposures and Behavioral Risk Factors with Head and Neck Cancer, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later)	1.85 (0.79, 4.33)	1.64 (0.73, 3.67)	1.47 (0.65, 3.30)	1.77 (0.77, 4.06)
Worked on Pile/in Pit (vs. Elsewhere)	1.24 (0.54, 2.85)	1.15 (0.51, 2.56)	1.41 (0.64, 3.11)	1.25 (0.56, 2.79)
Duration of WTC Work, [a] per 30 days	0.92 (0.82, 1.04)	0.93 (0.82, 1.05)	0.92 (0.82, 1.04)	0.94 (0.84, 1.06)
Protective Services Occupation (vs. Other)	2.51 (1.09, 5.82)	2.21 (0.99, 4.96)	2.27 (1.00, 5.14)	2.53 (1.10, 5.83)
Years of Cigarette Smoking, per 1 SD	1.78 (1.04, 3.03)	1.54 (0.95, 2.49)	1.24 (1.00, 1.56)	1.72 (1.04, 2.85)
Cumulative Alcohol Consumption, [b] per 1 SD	0.68 (0.42, 1.11)	0.78 (0.50, 1.23)	1.02 (0.90, 1.16)	0.76 (0.49, 1.17)
6 or more sex partners (vs. < 6)	1.20 (0.50, 2.86)	1.23 (0.57, 2.65)	[c]	2.92 (1.15, 7.46)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; SD, standard deviation (per case distribution); All models account for the matched design and are adjusted for race/ethnicity

[a] Duration was defined as number of days between first and last day on site

[b] Cumulative alcohol consumption was defined as: (average number of drinks per week) × (years of consumption)

[c] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 5: Interaction of Effects in Modeling Odds of Head and Neck Cancer, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later) [a]				
Among Protective Services	1.18 (0.42, 3.33)	1.10 (0.40, 3.00)	0.93 (0.35, 2.50)	1.02 (0.37, 2.85)
Among Other Occupations	3.77 (1.00, 14.11)	3.02 (0.86, 10.64)	3.26 (0.88, 12.13)	4.43 (1.14, 17.25)
Duration of work, per 30 days [b]				
Among those who worked on the pile/pit	1.06 (0.89, 1.26)	1.05 (0.87, 1.24)	1.01 (0.86, 1.20)	1.04 (0.87, 1.24)
Among those who worked elsewhere	0.82 (0.69, 0.98)	0.84 (0.71, 1.00)	0.85 (0.72, 1.00)	0.87 (0.75, 1.02)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; All models account for the matched design

[a] P-value for interaction: Model 1: 0.1616, Model 2: 0.2078, Model 3: 0.1257, Model 4: 0.0813; Models adjusted for race/ethnicity, duration of work (first to last day), work location (on the pile/pit vs. elsewhere), years of cigarette smoking, cumulative alcohol consumption (average drinks per week × years of drinking), and number of sex partners (6 or more vs. fewer than 6)

[b] P-value for interaction: Model 1: 0.0422, Model 2: 0.0750, Model 3: 0.1128, Model 4: 0.1328; Models adjusted for race/ethnicity, date of arrival (on 9/11 vs. later), occupational group (protective services vs. other), years of cigarette smoking, cumulative alcohol consumption (average drinks per week × years of drinking), and number of sex partners (6 or more vs. fewer than 6)

Table 6: Impact of Modeling an Alternate Measure of Tobacco Smoking Behavior, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later)	1.87 (0.81, 4.35)	1.63 (0.73, 3.63)	1.34 (0.62, 2.92)	1.74 (0.77, 3.91)
Worked on Pile/in Pit (vs. Elsewhere)	1.13 (0.50, 2.58)	1.06 (0.48, 2.34)	1.20 (0.56, 2.58)	1.17 (0.54, 2.55)
Duration of WTC Work, [a] per 30 days	0.93 (0.83, 1.05)	0.93 (0.83, 1.05)	0.93 (0.83, 1.05)	0.95 (0.85, 1.07)
Protective Services Occupation (vs. Other)	2.45 (1.03, 5.81)	2.01 (0.91, 4.45)	2.21 (0.99, 4.90)	2.24 (0.99, 5.05)
Pack-Years of Cigarette Smoking, [b] per 1 SD	1.79 (1.07, 3.00)	1.34 (0.89, 2.02)	1.09 (0.77, 1.54)	1.24 (0.88, 1.73)
Cumulative Alcohol Consumption, [c] per 1 SD	0.72 (0.43, 1.18)	0.86 (0.56, 1.34)	1.05 (0.93, 1.19)	0.81 (0.51, 1.28)
6 or more sex partners (vs. < 6)	1.18 (0.50, 2.78)	1.24 (0.58, 2.67)	[d]	2.62 (1.04, 6.64)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; SD, standard deviation (per case distribution); All models account for the matched design and are adjusted for race/ethnicity

[a] Duration defined as number of days between first and last day on site

[b] Pack-years was defined as: (average number of packs per day) × (years of smoking)

[c] Cumulative alcohol consumption was defined as: (average number of drinks per week) x (years of consumption)

[d] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 7: Impact of Modeling Years of Drinking to Measure Alcohol Consumption, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later)	1.64 (0.71, 3.79)	1.54 (0.68, 3.49)	1.42 (0.63, 3.22)	1.71 (0.75, 3.94)
Worked on Pile/in Pit (vs. Elsewhere)	1.28 (0.56, 2.88)	1.08 (0.48, 2.42)	1.39 (0.63, 3.07)	1.21 (0.53, 2.72)
Duration of WTC Work, [a] per 30 days	0.92 (0.82, 1.04)	0.92 (0.82, 1.04)	0.92 (0.82, 1.03)	0.94 (0.84, 1.05)
Protective Services Occupation (vs. Other)	2.54 (1.10, 5.89)	2.11 (0.94, 4.74)	2.32 (1.03, 5.24)	2.46 (1.07, 5.64)
Years of Cigarette Smoking, per 1 SD	1.51 (0.96, 2.38)	1.37 (0.90, 2.09)	1.28 (1.02, 1.60)	1.53 (0.97, 2.44)
Years of Alcohol Consumption, per 1 SD	0.77 (0.52, 1.14)	0.82 (0.54, 1.24)	0.85 (0.58, 1.25)	0.77 (0.50, 1.20)
6 or more sex partners (vs. < 6)	1.05 (0.45, 2.47)	1.22 (0.56, 2.62)	[b]	3.12 (1.20, 8.12)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; SD, standard deviation (per case distribution); All models account for the matched design and are adjusted for race/ethnicity

[a] Duration was defined as number of days between first and last day on site

[b] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 8: Impact of Modeling Total Binge Drinking Days to Measure Alcohol Consumption, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later)	1.92 (0.83, 4.43)	1.67 (0.75, 3.72)	1.41 (0.65, 3.06)	1.72 (0.77, 3.84)
Worked on Pile/in Pit (vs. Elsewhere)	1.29 (0.57, 2.91)	1.18 (0.54, 2.59)	1.18 (0.55, 2.53)	1.17 (0.53, 2.55)
Duration of WTC Work, [a] per 30 days	0.93 (0.82, 1.04)	0.93 (0.83, 1.05)	0.92 (0.82, 1.03)	0.94 (0.84, 1.06)
Protective Services Occupation (vs. Other)	2.95 (1.21, 7.22)	2.28 (1.02, 5.10)	2.03 (0.91, 4.50)	2.31 (1.02, 5.25)
Years of Cigarette Smoking, per 1 SD	1.86 (1.10, 3.16)	1.65 (1.01, 2.68)	1.25 (1.00, 1.58)	1.67 (1.02, 2.73)
Total Binge Drinking Days, [b] per 1 SD	0.69 (0.44, 1.07)	0.75 (0.49, 1.13)	0.96 (0.66, 1.41)	0.82 (0.56, 1.21)
6 or more sex partners (vs. < 6)	1.22 (0.52, 2.87)	1.32 (0.61, 2.83)	[c]	2.57 (1.02, 6.51)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; SD, standard deviation (per case distribution); All models account for the matched design and are adjusted for race/ethnicity

[a] Duration was defined as number of days between first and last day on site

[b] Binge drinking was defined as consumption of at least 4 (for women) or 5 (for men) in a single day

[c] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 9: Impact of Survey Mode on Regression Model Results, WTC Cancer Risk Epidemiology Study

	Model 1: Lifetime Behaviors	Model 2: Pre-WTC Exposure Behaviors	Model 3: During-WTC Exposure Behaviors	Model 4: Post-WTC Exposure Behaviors
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on 9/11 (vs. later)	2.02 (0.85, 4.82)	1.76 (0.77, 4.03)	1.49 (0.66, 3.37)	1.78 (0.78, 4.10)
Worked on Pile/in Pit (vs. Elsewhere)	1.20 (0.52, 2.80)	1.14 (0.50, 2.60)	1.41 (0.64, 3.11)	1.25 (0.56, 2.80)
Duration of WTC Work, [a] per 30 days	0.92 (0.81, 1.03)	0.93 (0.82, 1.04)	0.92 (0.82, 1.04)	0.94 (0.84, 1.06)
Protective Services Occupation (vs. Other)	2.95 (1.23, 7.06)	2.60 (1.12, 6.06)	2.36 (1.02, 5.46)	2.78 (1.17, 6.58)
Years of Cigarette Smoking, per 1 SD	1.73 (1.03, 2.93)	1.51 (0.93, 2.44)	1.24 (0.98, 1.56)	1.68 (1.01, 2.78)
Cumulative Alcohol Consumption, [b] per 1 SD	0.67 (0.41, 1.11)	0.79 (0.49, 1.27)	1.03 (0.90, 1.16)	0.77 (0.0.50, 1.19)
6 or more sex partners (vs. < 6)	1.31 (0.54, 3.18)	1.35 (0.61, 3.00)	[c]	2.88 (1.12, 7.41)
Survey Mode (Web vs. Phone)	2.06 (0.80, 5.35)	1.94 (0.76, 4.97)	1.21 (0.49, 2.99)	1.46 (0.59, 3.57)

Note: WTC, World Trade Center; OR, odds ratio; CI, confidence interval; SD, standard deviation (per case distribution); All models account for the matched design and are adjusted for race/ethnicity

[a] Duration was defined as number of days between first and last day on site

[b] Cumulative alcohol consumption was defined as: (average number of drinks per week) × (years of consumption)

[c] Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center

Table 10: Comparison of Demographic and WTC-Related Exposure Characteristics Between Participating and Non-Participating Cases, WTC Cancer Risk Epidemiology Study

Characteristic	Participating Cases (n=64)	Non-Participating Cases (n=38)	P-Value [a]
Demographics			
Age on 9/11, mean ± SD	41.9 ± 6.8	45.9 ± 10.6	0.0419
Sex, n (%)			
Male	57 (89.1)	38 (100)	0.0346
Female	7 (10.9)	0 (0)	
Race, n (%)			
Non-Hispanic white	53 (82.8)	31 (83.8)	0.9000
Other	11 (17.2)	6 (16.2)	
WTC Exposure Measures			
Date of Arrival on Site, n (%)			
9/11	31 (49.2)	14 (37.8)	0.2699
9/12 or Later	32 (50.8)	23 (62.2)	
Work Location, n (%)			
On the pile/in the pit	26 (41.3)	13 (35.1)	0.5437
Elsewhere	37 (58.7)	24 (64.9)	
Duration of WTC Work, mean ± SD [b]	117.9 ± 101.8	133.7 ± 101.5	0.4627
Total Days Worked/Volunteered, mean ± SD [c]	72.7 ± 77.5	59.3 ± 61.7	0.3721

Note: WTC, World Trade Center; SD, standard deviation; Counts may not sum to group total due to item nonresponse

[a] Chi square test for comparison of proportions or t-test for comparison of means

[b] Duration was defined as number of days between first and last day on site

[c] Total days was defined as the actual number of days on site, excluding days not on site

REFERENCES

1. Landrigan PJ, Lioy PJ, Thurston G, et al. Health and environmental consequences of the world trade center disaster. *Environ Health Perspect.* 2004;112(6):731-739.
2. Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives.* 2002;110(7):703-714.
3. Pleil JD, Vette AF, Johnson BA, Rappaport SM. Air levels of carcinogenic polycyclic aromatic hydrocarbons after the World Trade Center disaster. *Proc Natl Acad Sci U S A.* 2004;101(32):11685-11688.
4. Cohen MD, Vaughan JM, Garrett B, et al. Acute high-level exposure to WTC particles alters expression of genes associated with oxidative stress and immune function in the lung. *J Immunotoxicol.* 2015;12(2):140-153.
5. Graber JM, Harris G, Black K, et al. Excess HPV-related head and neck cancer in the world trade center health program general responder cohort. *Int J Cancer.* 2018.
6. Solan S, Wallenstein S, Shapiro M, et al. Cancer incidence in world trade center rescue and recovery workers, 2001-2008. *Environ Health Perspect.* 2013;121(6):699-704.
7. Li JH, Cone JE, Kahn AR, et al. Association Between World Trade Center Exposure and Excess Cancer Risk. *Jama-Journal of the American Medical Association.* 2012;308(23):2479-2488.
8. Berthiller J, Straif K, Agudo A, et al. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-845.
9. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48(11):3282-3287.
10. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst.* 2007;99(10):777-789.
11. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part E: Personal habits and indoor combustions.* Vol 100E; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
12. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF. Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. *Cancer Causes Control.* 2013;24(4):649-664.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part C: Arsenic, metals, fibres, and dusts.* Vol 100C; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
14. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. *N Engl J Med.* 2007;356:1944-1956.

15. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):467-475.
16. Langevin SM, McClean MD, Michaud DS, Eliot M, Nelson HH, Kelsey KT. Occupational dust exposure and head and neck squamous cell carcinoma risk in a population-based case-control study conducted in the greater Boston area. *Cancer Med.* 2013;2(6):978-986.
17. Feldman JG, Hazan M. A case-control investigation of alcohol, tobacco, and diet in head and neck cancer. *Prev Med.* 1975;4(4):444-463.
18. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res.* 1990;50(20):6502-6507.
19. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev.* 2009;18(2):541-550.
20. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9(1):e86023.
21. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol.* 2010;39(1):166-181.
22. Dasaro CR, Holden WL, Berman KD, et al. Cohort Profile: World Trade Center Health Program General Responder Cohort. *Int J Epidemiol.* 2017;46(2):e9.
23. Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. *Int J Epidemiol.* 2012;41(5):1480-1489.
24. ACS (American Cancer Society). *Cancer Facts & Figures 2017.* Atlanta, GA: American Cancer Society; 2017.
25. National Center for Health Statistics. National Health Interview Survey, 2015. Public-use data file and documentation. 2016; https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.
26. CDC (Centers for Disease Control and Prevention). 2016 Behavioral Risk Factor Surveillance System Questionnaire. 2015; https://www.cdc.gov/brfss/questionnaires/index.htm.
27. Zhou J, Michaud DS, Langevin SM, McClean MD, Eliot M, Kelsey KT. Smokeless tobacco and risk of head and neck cancer: evidence from a case-control study in New England. *Int J Cancer.* 2013;132(8):1911-1917.
28. Divaris K, Olshan AF, Smith J, et al. Oral health and risk for head and neck squamous cell carcinoma: the Carolina Head and Neck Cancer Study. *Cancer Causes Control.* 2010;21(4):567-575.
29. Collins D. Pretesting survey instruments: an overview of cognitive methods. *Qual Life Res.* 2003;12(3):229-238.
30. Liu Y, Pleasants RA, Croft JB, et al. Smoking duration, respiratory symptoms, and COPD in adults aged >/=45 years with a smoking history. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1409-1416.

31. Lubin JH, Albanes D, Hoppin JA, et al. Greater Coronary Heart Disease Risk With Lower Intensity and Longer Duration Smoking Compared With Higher Intensity and Shorter Duration Smoking: Congruent Results Across Diverse Cohorts. *Nicotine Tob Res.* 2017;19(7):817-825.
32. Friesema IH, Veenstra MY, Zwietering PJ, Knottnerus JA, Garretsen HF, Lemmens PH. Measurement of lifetime alcohol intake: utility of a self-administered questionnaire. *Am J Epidemiol.* 2004;159(8):809-817.
33. Woskie SR, Kim H, Freund A, et al. World Trade Center disaster: assessment of responder occupations, work locations, and job tasks. *Am J Ind Med.* 2011;54(9):681-695.
34. Brown LM, Mason TJ, Pickle LW, et al. Occupational risk factors for laryngeal cancer on the Texas Gulf Coast. *Cancer Res.* 1988;48(7):1960-1964.
35. Ahrens W, Jockel KH, Patzak W, Elsner G. Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. *Am J Ind Med.* 1991;20(4):477-493.
36. Merletti F, Boffetta P, Ferro G, Pisani P, Terracini B. Occupation and cancer of the oral cavity or oropharynx in Turin, Italy. *Scand J Work Environ Health.* 1991;17(4):248-254.
37. Paget-Bailly S, Guida F, Carton M, et al. Occupation and head and neck cancer risk in men: results from the ICARE study, a French population-based case-control study. *J Occup Environ Med.* 2013;55(9):1065-1073.
38. Lubin JH, Purdue M, Kelsey K, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol.* 2009;170(8):937-947.
39. Welch AE, Jasek JP, Caramanica K, Chiles MC, Johns M. Cigarette smoking and 9/11-related posttraumatic stress disorder among World Trade Center Health Registry enrollees, 2003-12. *Prev Med.* 2015;73:94-99.
40. Zvolensky MJ, Farris SG, Kotov R, et al. Posttraumatic stress symptoms and smoking among World Trade Center disaster responders: A longitudinal investigation. *Compr Psychiatry.* 2015;63:46-54.
41. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part B: Biological Agents.* Vol 100B; IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 2012.
42. Dahlstrom KR, Li G, Tortolero-Luna G, Wei Q, Sturgis EM. Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites. *Head Neck.* 2011;33(6):847-855.
43. Schnelle C, Whiteman DC, Porceddu SV, Panizza BJ, Antonsson A. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. *Int J Cancer.* 2017;140(5):1027-1034.
44. Chaturvedi AK, Graubard BI, Broutian T, et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. *Cancer Res.* 2015;75(12):2468-2477.

45. Dahlgren L, Dahlstrand HM, Lindquist D, et al. Human papillomavirus is more common in base of tongue than in mobile tongue cancer and is a favorable prognostic factor in base of tongue cancer patients. *Int J Cancer.* 2004;112(6):1015-1019.
46. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer.* 2006;119(11):2620-2623.
47. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old [press release]. Silver Spring, MD: United States Food and Drug Administration2018.
48. Chaturvedi AK, Graubard BI, Broutian T, et al. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. *J Clin Oncol.* 2018;36(3):262-267.
49. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst.* 2007;99(23):1801-1810.
50. Dillman DA, Smyth JD, Christian LM, Dillman DA. *Internet, mail, and mixed-mode surveys : the tailored design method.* 3rd ed. Hoboken, N.J.: Wiley & Sons; 2009.
51. CDC-WTCHP. Minimum Latency & Types or Categories of Cancer. 2015; https://www.cdc.gov/wtc/pdfs/policies/WTCHP-Minimum-Cancer-Latency-PP-01062015-508.pdf. Accessed February 15, 2019.
52. Wisnivesky JP, Teitelbaum SL, Todd AC, et al. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. *Lancet.* 2011;378(9794):888-897.
53. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Statistics. https://seer.cancer.gov/statistics/summaries.html. Accessed Aug. 11, 2017.
54. Murphy BA, Deng J. Advances in Supportive Care for Late Effects of Head and Neck Cancer. *J Clin Oncol.* 2015;33(29):3314-3321.

DISTRIBUTION OF RISK FACTORS FOR HEAD AND NECK CANCER SUBTYPES AMONG WORLD TRADE CENTER RESPONDERS: A CASE-CASE STUDY

By

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Manuscript 3 of 3 of a dissertation entitled

MEASUREMENT AND EVALUATION OF RISK FACTORS FOR CANCERS OF THE HEAD AND NECK IN A COHORT OF 9/11 WORLD TRADE CENTER RESPONDERS

Submitted to the

School of Public Health

And the

Graduate School – New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Written under the direction of

Judith M. Graber, PhD, MS

ABSTRACT

Background: Risk factors for head and neck cancer (HNC) vary by subtype in the general population based on human papillomavirus (HPV) positivity; oral cavity and laryngeal cancers are typically HPV-negative and strongly associated with older age and tobacco and alcohol use, while HPV-positive oropharyngeal cancers tend to be diagnosed at younger ages and are associated with sexual behavior. We used a case-case approach to assess whether risk factors differ by cancer site in a population of WTC responders.

Methods: We compared WTC-related and behavioral risk factors over the lifetime and before, during, and after the WTC response by cancer site: oropharynx (n=28), oral cavity (n=13), larynx (n=11) and other HNC (n=12). We assessed differences of means using analysis of variance and of proportions using chi-square or Fisher's exact tests. We used multinomial logistic regression models to assess multivariable associations with cancer subtype, with oropharyngeal cancers as the referent group.

Results: Proportion of cases in protective services occupations and prevalence of tonsillectomy varied significantly by cancer site (p=0.0008 and p=0.0390, respectively), with both being highest among oropharyngeal cancer cases. Lifetime and post-WTC cumulative alcohol consumption differed significantly by cancer site, with highest means observed for laryngeal cancer cases (p=0.0353 and p=0.0063, respectively). In multivariable models, post-WTC cumulative alcohol consumption was positively and significantly associated with odds of laryngeal as opposed to oropharyngeal cancer (OR: 2.04, 95% CI: 1.07, 3.87). WTC exposures did not differ by HNC site, nor did age at sexual debut or number of sex partners.

Discussion: Distribution of risk factors for HNC subtypes varies with respect to occupation and alcohol consumption, but not age, tobacco use, or sexual behavior. Results suggest certain risk factors for HNC among WTC-exposed populations may differ from that observed in the general population and highlight a need for additional research on HNC subtypes in this population.

INTRODUCTION

Responders to the World Trade Center (WTC) disaster faced possible exposure to multiple human carcinogens, making cancer a plausible health consequence of participation in the WTC rescue, recovery, and cleanup efforts.[1,2] A recent analysis of World Trade Center Health Program (WTCHP) General Responder Cohort (GRC) members found an excess of head and neck (HNC) cancers in this population relative to the general population.[3] Our subsequent nested case-control study of HNC among GRC members found increased excess estimated risk for HNC associated with occupation in the protective services, increased years of cigarette smoking, and increased number of sex partners after the WTC response, as well as increased risk for non-protective services workers who arrived on 9/11 as opposed to later (see Manuscript 2).

The epidemiology of HNC is evolving in concert with changes in the prevalence of risk factors such as tobacco use, alcohol use, and persistent oral infection with oncogenic human papillomavirus (HPV), with HPV-positive and HPV-negative HNCs emerging as distinct cancer groups.[4-6] Whereas HPV-negative HNCs typically occur among elderly adults and are strongly associated with tobacco and alcohol use, incidence of HPV-positive HNC is increasing among middle-aged adults, particularly non-Hispanic white men, without significant history of smoking and drinking.[5,7-9] HPV is primarily associated with cancers of the oropharynx, including the tonsils and base of tongue,[10] thus the increasing incidence of HPV infection is likely the predominant driver of the increasing incidence of oropharyngeal cancers.[11,12] Survival rates for HPV-associated HNCs are generally better than those not associated with HPV,[13] and HPV-seropositive status is a well-documented positive prognostic indicator,[13-20] further distinguishing HPV-positive from other HNC tumors.

Several measures of sexual behavior are associated with HPV infection as well as incidence of HPV-positive HNC. For example, D'Souza and colleagues[8,21] observed significant positive associations between number of oral and vaginal sex partners and odds of HPV-positive oropharyngeal cancer, and Zevallos and colleagues found positive associations between number of sexual partners and odds of oropharyngeal cancer.[22] Additional studies have found HPV risk to be significantly associated with number of sex partners, with risk for infection increasing with number of partners in a dose-response fashion.[21,23-26] Taken together, this body of research suggests that assessing sexual behavior history is a reasonable surrogate measure for oral HPV infection.

Additional oral health factors may play a role in HPV-associated HNCs, including history of tonsillectomy and poor dentition. Zevallos and colleagues[22] observed negative associations between tonsillectomy and tonsillar cancer, with stronger associations observed when restricting to HPV-positive tumors. D'Souza and colleagues noted a strong and positive association between tooth loss and oropharyngeal cancer,[8] and several international case-control studies of HNC noted increased risk for oropharyngeal cancer associated with poor dentition.[27-29]

Given the differences in site-specific risk factor profiles in the general population, we sought to examine whether the same is true for WTC-exposed persons with HNC. We performed a case-case comparison of WTCHP GRC members with HNC to assess whether behavioral risk factor profiles differ by site, hypothesizing that the profiles for oral cavity and laryngeal cancer would include increased tobacco and alcohol use while the profile for oropharyngeal cancer would instead include increased number of sex partners, and to explore whether association with WTC exposures varies by cancer site.

METHODS

Study Population

We analyzed data collected from case participants of the WTC-Cancer Risk Epidemiology Study (WTC-CARES), designed as a nested case-control study of HNC among WTCHP GRC members. As previously described (see Manuscript 2), eligible cases were living GRC members diagnosed of HNC between 2002 and 2016 (International Classification of Disease [ICD]-9 codes 140-149.9, 160-161.0; ICD-10 codes C00.0-C14.9, C32-C32.9). Of 94 eligible cases, 64 (68.1%) consented to participate. Based on what is known about the etiologies of HNC sites, we categorized participants into four cancer site groups: oropharyngeal (base of tongue, tonsil, other oropharynx), oral cavity (tongue, gum, palate, other oral cavity and pharynx), larynx, and other (nasopharynx, nasal cavity and middle ear, accessory sinuses, parotid gland, other major salivary glands).

Recruitment and Data Collection

As previously described, (see Manuscript 2) recruitment began in July 2017 and data collection continued for nine months. Prospective participants received a letter with information about WTC-CARES and how to schedule a telephone interview or complete the survey online. Telephone was the preferred mode of survey administration, but we offered the web-based option, because common sequelae of HNC include impaired speech. Specially-trained study interviewers then attempted to contact potential participants and administer the questionnaire via telephone or guide towards online participation.

WTC Exposure Measures

We requested and obtained deidentified WTC exposure data for study participants from the WTCHP General Responder Data Center (GRDC), including date of arrival to the WTC effort, primary work location during key phases of the WTC effort (September 2001, October 2001, November through December 2001, and January through June 2002), duration of WTC work (first and last days of work), and total days of WTC work. We categorized date of arrival as arrival on 9/11/2001 or arrival on 9/12/01 or later. We categorized primary work location into two groups using a tiered approach. Participants who spent the majority of at least one phase of the WTC effort "on the pile/in the pit" were classified as "on the pile"; participants who did not spend time on the pile were classified as "elsewhere."

Behavioral Risk Factor Measures

As previously described, (see Manuscript 1) we developed the WTC-CARES questionnaire based on review of standardized instruments[30,31] and other retrospective studies of HNC[32,33] and evaluated validity and cultural appropriateness via expert review and several rounds of cognitive interviewing.[34] The final questionnaire assessed behavioral risk factors, including frequency and duration of tobacco and alcohol use, sexual behavior history, and oral health history, during each of three time periods: 1) before WTC exposure, 2) during WTC exposure, and 3) after WTC exposure until HNC diagnosis. The length of each period varied by participant based on their age of behavior initiation (e.g., age began smoking cigarettes), age during their participation in the WTC response, and age at diagnosis.

We selected years of cigarette smoking as our primary measure of tobacco use given prior research associating long-term infrequent smoking with increased HNC risk.[35] We estimated years of smoking during each study period based on age of initiation, age on 9/11, and age of diagnosis or cessation, if cessation occurred before diagnosis, less any number of years during each period that the participant reported not smoking. For example, if a person reported smoking onset at age 20 and was 40 on 9/11 but reported not smoking for 5 years between ages 20 and 40, we estimated this person's smoking duration as 40 – 20 – 5 = 15 years. We summed years of smoking across all three study periods to estimate lifetime years of smoking. We used the same approach to estimate years of alcohol consumption.

We calculated average frequency of alcohol consumption during each study period by multiplying usual frequency of alcohol consumption by the usual quantity per drinking occasion (as described by Friesema et al.[36]). Since each study period varied in length by participant, we then multiplied this measure by the estimated years of alcohol consumption to create a cumulative alcohol consumption index. We summed indices across study periods to estimate lifetime cumulative alcohol consumption.

We assessed number of sex partners over the lifetime and during each study period using period-specific questions with categorical response options (e.g., *Between [last day of WTC work] and [diagnosis month/year], how many different sexual partners* *have you had? Please count every partner, even those you were with only once. By 'sex' we mean sexual intercourse, oral sex, or anal sex. 0 partners, 1 partner, 2 to 5 partners, 6 to 10 partners, 11 to 15 partners, 16 to 25 partners, 26 to 50 partners, 51 to 100 partners, more than 100 partners*). We assigned the median number of a participant's selection (e.g., 3.5 for a response of 2 to 5 partners) to create a continuous variable for analysis.

Participants indicated a history of tooth loss with an affirmative response to the question, "Have you ever had any permanent teeth extracted due to gum disease, gingivitis, or decay?" and history of tonsillectomy with an affirmative response to the question, "Have you had your tonsils removed?"

We assessed primary lifetime occupation with the WTC-CARES questionnaire and classified participants as protective services (e.g., police officers), construction and cleanup, mechanics and machinists, communications technicians, and other. Based on the distribution, we further grouped participants as protective services or other for analysis.

Protection of Human Subjects

The Health Sciences Institutional Review Board at Rutgers University reviewed and approved the study protocol, including recruitment, consent, and data collection procedures (Pro20160001045). This included details of an Honest Broker agreement, whereby a designated entity maintained all protected health information (PHI) for WTC-CARES. We received only deidentified survey data that included a unique ID number, and the WTCHP data we obtained from the GRDC included the same ID number. We then merged the two data sources by this variable. The Honest Broker agreement was also outlined in our Data Use Agreement (DUA) between Rutgers University and the GRDC. We additionally obtained a certificate of confidentiality from the CDC.

Statistical Analysis

We compared participant characteristics and risk factors by cancer site group using Wald chi-square tests (for categorical variables) or ANOVA (for continuous variables). In the case of sparse cells, we assessed dependence using Fisher's Exact tests. We also assessed potential selection bias by comparing cases enrolled to those identified but not enrolled. We then used multivariable multinomial logistic regression to model the associations between cancer site and WTC exposure duration and behavioral risk factors, with oropharyngeal cancers as the referent group. Since all participants in the laryngeal cancer group were non-Hispanic white males, we restricted regression analyses to non-Hispanic white males (n=48). Given the small sample size, we prioritized parsimony when considering covariate inclusion, retaining the WTC exposure variable (duration of WTC work) that yielded the lowest Akaike information criterion [AIC] when included. We further excluded history of tooth loss and tonsillectomy from the regression analyses, because their inclusion prevented model convergence.

Sensitivity analyses included substituting alternate measures of behavior (e.g., total binge drinking days in place of cumulative alcohol consumption) and assessing the impact of survey mode.

We suppressed cell counts less than 5 as per the terms of our data use agreement with the WTCHP DRC. All statistical tests were two-sided with p-values less than 0.05 considered indicative of statistical significance and p-values less than 0.1 considered suggestive of an association. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) for all analyses.

RESULTS

Age at diagnosis ranged from 49.3 (other sites) to 54.8 (oral cavity) but did not differ significantly by cancer site (p=0.2350; Table 1). All four groups were predominantly male and non-Hispanic white and did not vary by average body mass index (BMI). The proportion of persons working in the protective services varied significantly by cancer site (p=0.008), with the lowest observed among those with laryngeal cancer (<45.5%). We were not able to assess exposure to specific occupational exposures by cancer site due to small numbers (data not shown). No WTC exposure measures varied significantly by cancer site, although both duration of work and total days of work were lowest for the laryngeal cancer group. There were no significant differences in ever smoking, drinking, or binge drinking prevalence, nor in age at sexual debut or lifetime number of sex partners. History of tonsillectomy differed significantly by cancer site (p=0.0390), with the highest prevalence observed among the oropharyngeal cancer group (53.6%). Tooth loss prevalence did not differ by cancer site group.

Lifetime years of smoking, cumulative alcohol consumption, and total binge drinking days were highest in the laryngeal cancer group, and both lifetime and post-WTC cumulative alcohol consumption differed significantly by cancer site group (Table 2). Number of sex partners during each study period was generally highest among those with laryngeal cancer, however these differences were not statistically significant.

Odds of having a protective services occupation were significantly lower for the laryngeal cancer group than the oropharyngeal cancer group (Table 3), but we found no significant associations between cancer site and lifetime years of smoking, cumulative alcohol consumption, lifetime number of sex partners, or duration of WTC work. However, when considering behaviors prior to the WTC study period (Table 4), increased number of lifetime sex partners was suggestively associated with increased odds of laryngeal as opposed to oropharyngeal cancer (OR: 1.13, 95% CI: 1.00, 1.29). When considering post-WTC behaviors (Table 5), an increase of 30 cumulative alcohol consumption units (equivalent to 2 years of consuming 15 drinks per week) was associated with increased odds of laryngeal as opposed to oropharyngeal cancer (OR: 2.04, 95% CI: 1.07, 3.87).

Other than gender distribution (all non-participants were male, p=0.0439), we saw no statistical differences in demographics, cancer site distribution, or WTC exposure measures between cases who did and did not enroll in WTC-CARES (Table 6).

Our sensitivity analyses found no association between survey mode (telephone vs. web) by cancer site (p=0.7606, data not shown). When substituting total binge drinking days for cumulative alcohol consumption, effect estimates were similar (Table 7).

DISCUSSION

In this case-case study of WTCHP GRC members with HNC, we compared risk factors and WTC exposures amongst oropharyngeal, oral cavity, laryngeal, and other HNC site groups. We found significant bivariate associations with occupational group, history of tonsillectomy, and lifetime and post-WTC cumulative alcohol consumption but no significant differences in WTC exposures, occupational exposures, duration of cigarette smoking, sexual behavior history, or history of tooth loss. Compared to oropharyngeal cancers cases, laryngeal cancer cases had lower odds of having a protective services occupation, but greater odds of increased cumulative alcohol consumption after their involvement in the WTC response.

Our finding of increased alcohol consumption among laryngeal cancer cases relative to oropharyngeal cancers cases aligns with prior research finding null or weak associations between heavy alcohol consumption and HPV-positive oropharyngeal cancers.[7,8] We also found higher tonsillectomy rates among oropharyngeal cancers, which is consistent the work by Zevallos and colleagues, who found a positive association between tonsillectomy and certain oropharyngeal cancers (i.e., base of tongue but not tonsillar) that were HPV-positive.[22] However, we found no significant association between number of sex partners and HNC site, which is inconsistent with prior studies finding increased sexual activity associated with increased oropharyngeal and HPV-positive HNC risk.[8,37] This discrepancy may be due to underreporting of sexual behavior in our study population but also raises questions as to whether oropharyngeal cancers among WTC-exposed populations are somehow different from those in the general population.

Our finding of differential occupational profiles between cancer sites was surprising and warrants further study. Importantly, we could not examine occupation beyond protective services vs. other; other may include professions that are associated with specific occupational exposures. If these include exposures known to be associated with risk for laryngeal cancer specifically, this may explain the significantly lower odds of laryngeal relative to oropharyngeal cancer seen for protective services occupations. However, we could not examine specific occupational exposures to support or oppose this explanation due to small numbers.

We did not find significant differences in prevalence or duration of cigarette smoking by cancer site, which is inconsistent with research in the general population attributing tobacco use to oral cavity and laryngeal cancers but not HPV-associated oropharyngeal cancers. We also did not find significant differences in age at diagnosis, although HPV-associated HNCs tend to occur at younger ages than HPV-unassociated HNCs in the general population. Moreover, average age at diagnosis was under 55 years for all cancer sites, whereas the average age of HNC diagnosis in the general population (63 years[38]). Although the age distributions of GRC members and the general population are different, this suggests a potential reduction in latency for WTC-exposed cancers of the head and neck.

There are several limitations to note. First, the small number of cases limited our ability to perform more refined analyses of occupation and limited statistical power. Additionally, since there were no non-white or female participants with laryngeal cancer, we restricted regression analyses to non-Hispanic white males, which further reduced sample size and prohibited examination of these demographic characteristics. Third, we did not have HPV status for cases and thus could not differentiate between HPV-positive and HPV-negative cancers, although number of sex partners is a well-established surrogate measure for HPV infection risk.[8,21,37] Finally, our results may be subject to selection bias, if cases who enrolled differ from those who did not. However, we did not find any differences in cancer site distribution between GRC members with HNC who did and did not participate in WTC-CARES.

Despite these limitations, we are the first to examine HNC risk factors by site among WTCHP GRC members, and our results suggest that HNC risk factor profiles may differ by site. We also found evidence suggesting that oropharyngeal cancers among WTC-exposed populations may differ from those in the general population, and that HNCs in WTC-exposed persons may be shorter than what is typical in the general population. Taken together, our findings highlight a need for additional research on HNC subtypes in this population, including assessment of HPV status in oropharyngeal and other HNC tumors.

Table 1: Characteristics of cases by cancer site, WTC Cancer Risk Epidemiology Study (N=64)

	Oropharynx n=28	Oral Cavity n=13	Larynx n=11	Other n=12	p-value
Demographics					
Age at Diagnosis, mean ± SD	51.5 ± 7.5	54.8 ± 9.4	54.6 ± 8.3	49.3 ± 4.7	0.2350 [c]
Male sex, n (%)	> 23 (>82.1)	> 8 (> 61.5)	11 (100.0)	> 7 (> 58.3)	0.2605 [d]
BMI at Diagnosis, mean ± SD	29.8 ± 4.5	28.1 ± 6.1	30.0 ± 6.2	32.0 ± 6.6	0.3876 [c]
Non-Hispanic white, n (%)	> 23 (>82.1)	> 8 (> 61.5)	10 (100.0)	7 (58.3)	0.0782 [d]
Protective Services Occupation, n (%)	20 (71.4)	8 (61.5)	* (<45.5)	> 7 (> 58.3)	0.0008 [d]
WTC Exposure Measures					
Age on 9/11, mean ± SD	41.9 ± 6.4	44.5 ± 8.1	43.9 ± 7.5	38.8 ± 4.4	0.1606 [c]
Arrived on 9/11, n (%)	17 (60.7)	5 (41.7)	6 (54.6)	* (< 41.7)	0.1956 [d]
Worked on the pile, n (%)	12 (42.9)	* (< 38.5)	5 (45.5)	5 (41.7)	0.9649 [d]
Duration of WTC work, mean ± SD [a]	118.4 ± 106.4	162.3 ± 97.8	71.6 ± 85.1	114.9 ± 101.1	0.2085 [c]
Total Days of work, mean ± SD [b]	70.7 ± 78.6	88.8 ± 83.1	49.9 ± 60.7	82.2 ± 86.6	0.6549 [c]
Risk Behaviors					
Ever cigarette smoker, n (%)	14 (50.0)	* (< 38.5)	> 6 (> 54.5)	7 (58.3)	0.2299 [e]
Ever alcohol drinker, n (%)	22 (78.6)	> 8 (> 61.5)	> 6 (> 54.5)	10 (83.3)	0.6710 [d]
Ever binge drinker, n (%)	15 (53.6)	* (< 38.5)	5 (45.5)	5 (41.7)	0.5839 [d]
Age at sexual debut, mean ± SD	17.3 ± 2.6	17.8 ± 2.6	17.2 ± 1.9	17.2 ± 3.3	0.9367 [c]
Lifetime sex partners, mean ± SD	8.6 ± 8.4	10.7 ± 9.7	20.2 ± 27.8	13.9 ± 20.3	0.2393 [c]
Oral Health History					
Tonsillectomy, n (%)	15 (53.6)	* (< 38.5)	5 (45.5)	* (< 41.7)	0.0390 [d]
Ever tooth loss, n (%)	5 (17.9)	* (< 38.5)	* (<45.5)	* (< 41.7)	0.5932 [d]

Note: WTC, World Trade Center; SD, standard deviation; BMI, body mass index (kg/m2);
*Cell counts < 5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center
[a] Duration of WTC work defined as number of days between first and last day of work
[b] Total days was defined as the actual number of days on site, excluding days not on site
[c] ANOVA (F); [d] Fisher's Exact Test; [e] Wald chi-square test

Table 2: Lifetime and Pre-, During-, and Post-WTC Risk Behaviors by Cancer Site, WTC Cancer Risk Epidemiology Study (N=64)

		Cancer Site				
Risk Factor	Time Period	Oropharynx n=28	Oral Cavity n=13	Larynx n=11	Other n=12	p-value[c]
Years of smoking, mean ± SD	Lifetime	9.8± 13.3	5.4± 10.1	18.3± 14.0	10.2± 10.2	0.0912
	Before WTC	8.4± 10.5	4.5± 7.9	14.4± 10.6	7.8± 8.1	0.1042
	During WTC	0.1± 0.2	0.0± 0.1	0.1± 0.3	0.1± 0.2	0.6311
	After WTC	1.4± 3.3	0.9± 2.3	3.8± 5.0	2.3± 4.4	0.2186
Cumulative Alcohol Consumption, mean ± SD	Lifetime	139.4± 168.8	54.4± 90.2	364.8± 592.6	78.1± 118.7	0.0353
	Before WTC	114.7± 152.9	45.6± 78.7	232.6± 422.0	53.5± 71.9	0.1274
	During WTC	1.9± 4.2	0.5± 1.3	1.6± 2.9	0.2± 0.4	0.3975
	After WTC	22.8± 35.2	8.4± 23.1	130.6± 198.1	28.9± 78.5	0.0063
Total Binge Drinking Days, mean ± SD	Lifetime	547.7± 840.9	225.5± 558.0	2804.0± 5934.3	473.2± 1076.5	0.0603
	Before WTC	464.4± 718.1	219.0± 552.7	1872.3± 4383.0	233.7± 714.3	0.1199
	During WTC	15.7± 40.1	4.3± 14.4	75.8± 146.3	0.2± 0.6	0.0281
	After WTC	100.8± 230.2	2.2± 7.8	855.9± 1538.6	239.3± 825.3	0.0250
Number of sex partners, mean ± SD	Lifetime	8.6± 8.4	10.7± 9.7	20.2± 27.8	13.9± 20.3	0.2393
	Before WTC	7.5± 8.3	9.8± 10.1	21.6± 28.9	9.6± 11.3	0.0727
	During WTC	1.2± 0.9	0.9± 0.3	1.2± 0.9	1.0± 0.9	0.8259
	After WTC	4.1± 7.8	7.5± 11.0	12.3± 23.5	4.8± 5.6	0.2906

Note: WTC, World Trade Center; SD, standard deviation
[a] Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption)
[b] Binge drinking was defined as consumption of 5 (for men) or 4 (for women) drinks in a single occasion
[c] ANOVA F test

Table 3: Odds of Oral Cavity, Laryngeal, or Other Head and Neck Cancer Relative to Oropharyngeal Cancer, Adjusted for Lifetime Risk Behaviors, WTC Cancer Risk Epidemiology Study (N=64)

	Oral Cavity		Larynx		Other	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Age at Diagnosis, year	1.09	(0.94, 1.26)	0.88	(0.73, 1.06)	0.87	(0.73, 1.05)
Protective Services (vs. other)	0.89	(0.09, 8.67)	0.05	(0.00, 1.00)	1.30	(0.13, 12.69)
Duration of WTC work, 30 days [a]	1.23	(0.86, 1.76)	0.78	(0.48, 1.27)	0.64	(0.38, 1.07)
Lifetime Duration of smoking, 5 years	0.93	(0.55, 1.58)	1.04	(0.62, 1.75)	1.09	(0.67, 1.76)
Lifetime Cumulative Alcohol Consumption, 30 units [b]	0.83	(0.63, 1.11)	1.12	(0.97, 1.28)	1.00	(0.85, 1.17)
Lifetime number of sex partners	0.99	(0.89, 1.09)	1.10	(0.98, 1.22)	1.08	(0.95, 1.22)

Note: WTC, World Trade Center; OR, adjusted odds ratio; CI, confidence interval; Restricted to non-Hispanic white males (n=48)

[a] Duration of WTC work defined as number of days between first and last day of work

[b] Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption)

Table 4: Odds of Oral Cavity, Laryngeal, or Other Head and Neck Cancer Relative to Oropharyngeal Cancer, Adjusted for Pre-WTC Risk Behaviors, WTC Cancer Risk Epidemiology Study (N=64)

	Oral Cavity		Larynx		Other	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Age at Diagnosis, year	1.10	(0.95 , 1.26)	0.81	(0.65 , 1.02)	0.88	(0.73 , 1.06)
Protective Services (vs. other)	0.94	(0.10 , 9.15)	0.04	(0.00 , 1.15)	1.19	(0.13 , 10.82)
Duration of WTC work, 30 days [a]	1.21	(0.86 , 1.71)	0.79	(0.47 , 1.34)	0.63	(0.37 , 1.07)
Pre-WTC Duration of smoking, 5 years	0.80	(0.40 , 1.63)	0.79	(0.39 , 1.60)	1.10	(0.60 , 2.01)
Pre-WTC Cumulative Alcohol Consumption, 30 units [b]	0.86	(0.63 , 1.19)	1.26	(0.96 , 1.67)	0.95	(0.72 , 1.27)
Pre-WTC number of sex partners	0.98	(0.89 , 1.08)	1.13	(1.00 , 1.29)	1.06	(0.94 , 1.21)

Note: WTC, World Trade Center; OR, adjusted odds ratio; CI, confidence interval; Restricted to non-Hispanic white males (n=48)

[a] Duration of WTC work defined as number of days between first and last day of work

[b] Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption)

Table 5: Odds of Oral Cavity, Laryngeal, or Other Head and Neck Cancer Relative to Oropharyngeal Cancer, Adjusted for Post-WTC Risk Behaviors, WTC Cancer Risk Epidemiology Study (N=64)

	Oral Cavity		Larynx		Other	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Age at Diagnosis, year	1.05	(0.92, 1.21)	0.84	(0.67, 1.07)	0.85	(0.69, 1.04)
Protective Services (vs. other)	0.65	(0.05, 8.09)	0.00	(0.00, 1.67)	0.70	(0.06, 8.84)
Duration of WTC work, 30 days [a]	1.26	(0.81, 1.95)	0.74	(0.42, 1.29)	0.61	(0.34, 1.09)
Post-WTC Duration of smoking, 5 years	0.42	(0.05, 3.38)	1.79	(0.12, 26.29)	0.91	(0.19, 4.36)
Post-WTC Cumulative Alcohol Consumption, 30 units [b]	0.00	(0.00, 19.82)	2.04	(1.07, 3.87)	1.30	(0.85, 2.00)
Post-WTC number of sex partners	0.97	(0.87, 1.08)	1.13	(0.97, 1.31)	1.10	(0.93, 1.30)

Note: WTC, World Trade Center; OR, adjusted odds ratio; CI, confidence interval; Restricted to non-Hispanic white males (n=48)

[a] Duration of WTC work defined as number of days between first and last day of work

[b] Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption)

Table 6: Comparison of Demographic and WTC-Related Exposure Characteristics Between Participating and Non-Participating Cases, WTC Cancer Risk Epidemiology Study (N=102)

	Enrolled (n=64)	Not Enrolled (n=38)	p-value[a]
Demographics			
Age at Diagnosis, mean ± SD	51.2 ± 7.3	54.1 ± 9.9	0.1421
Male sex, n (%)	57 (89.1)	38 (100.0)	0.0439
Non-Hispanic white, n (%)	53 (82.8)	31 (83.8)	0.9000
Cancer Site, n (%)			
Oropharynx	28 (43.8)	15 (41.7)	0.3768
Oral Cavity	13 (20.3)	< 5 (< 13.2)	
Larynx	11 (17.2)	11 (36.7)	
Other	12 (18.8)	6 (16.7)	
WTC Exposure Measures			
Arrived on 9/11, n (%)	31 (49.2)	14 (37.8)	0.2699
Work on the pile/in the pit, n (%)	26 (41.3)	13 (35.1)	0.5437
Duration of WTC Work, mean ± SD[b]	117.9 ± 101.8	133.7 ± 101.5	0.4627
Total Days Worked/Volunteered, mean ± SD[c]	72.7 ± 77.5	59.3 ± 61.7	0.3721

Note: WTC, World Trade Center; SD, standard deviation

[a] Chi square test for comparison of proportions or t-test for comparison of means

[b] Duration was defined as number of days between first and last day on site

[c] Total days was defined as the actual number of days on site, excluding days not on site

Table 7: Impact of Modeling Total Binge Drinking Days to Measure Alcohol Consumption, WTC Cancer Risk Epidemiology Study (N=64)

	Oral Cavity		Larynx		Other	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Age at Diagnosis, year	1.08	(0.94 , 1.24)	0.88	(0.73 , 1.06)	0.87	(0.72 , 1.05)
Protective Services (vs. other)	1.22	(0.14 , 10.76)	0.04	(0.00 , 0.97)	1.23	(0.12 , 12.20)
Duration of WTC work, 30 days [a]	1.15	(0.83 , 1.58)	0.82	(0.49 , 1.38)	0.64	(0.39 , 1.07)
Lifetime duration of smoking, 5 years	0.80	(0.48 , 1.32)	1.09	(0.66 , 1.80)	1.06	(0.67 , 1.67)
Lifetime binge drinking, 200 days [b]	0.95	(0.73 , 1.24)	1.11	(0.95 , 1.31)	1.04	(0.89 , 1.21)
Lifetime number of sex partners	0.99	(0.90 , 1.10)	1.09	(0.97 , 1.22)	1.07	(0.94 , 1.22)

Note: WTC, World Trade Center; OR, adjusted odds ratio; CI, confidence interval; Restricted to non-Hispanic white males (n=48)

[a] Duration of WTC work defined as number of days between first and last day of work

[b] Binge drinking was defined as consumption of 5 or more drinks in a single occasion; 200 days approximates 2 years of 15 drinks per week

REFERENCES

1. Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives.* 2002;110(7):703-714.
2. Landrigan PJ, Lioy PJ, Thurston G, et al. Health and environmental consequences of the world trade center disaster. *Environ Health Perspect.* 2004;112(6):731-739.
3. Graber JM, Harris G, Black K, et al. Excess HPV-related head and neck cancer in the world trade center health program general responder cohort. *Int J Cancer.* 2018.
4. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26(4):612-619.
5. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst.* 2008;100(6):407-420.
6. Nevens D, Nuyts S. HPV-positive head and neck tumours, a distinct clinical entity. *B-ENT.* 2015;11(2):81-87.
7. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst.* 2007;99(23):1801-1810.
8. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. *N Engl J Med.* 2007;356:1944-1956.
9. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol.* 2014;50(5):380-386.
10. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol.* 2004;31(6):744-754.
11. Katzel JA, Merchant M, Chaturvedi AK, Silverberg MJ. Contribution of demographic and behavioral factors on the changing incidence rates of oropharyngeal and oral cavity cancers in northern California. *Cancer Epidemiol Biomarkers Prev.* 2015;24(6):978-984.
12. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294-4301.
13. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol.* 2012;22(2):128-142.
14. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. *Oral Oncol.* 2014;50(6):565-574.
15. Dahlgren L, Dahlstrand HM, Lindquist D, et al. Human papillomavirus is more common in base of tongue than in mobile tongue cancer and is a favorable prognostic factor in base of tongue cancer patients. *Int J Cancer.* 2004;112(6):1015-1019.

16. Dahlstrand H, Nasman A, Romanitan M, Lindquist D, Ramqvist T, Dalianis T. Human Papillomavirus Accounts both for Increased Incidence and Better Prognosis in Tonsillar Cancer. *Anticancer Research.* 2008;28:1133-1138.
17. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol.* 2006;24(17):2606-2611.
18. Goodman MT, Saraiya M, Thompson TD, et al. Human papillomavirus genotype and oropharynx cancer survival in the United States of America. *Eur J Cancer.* 2015;51(18):2759-2767.
19. Salazar CR, Anayannis N, Smith RV, et al. Combined P16 and human papillomavirus testing predicts head and neck cancer survival. *Int J Cancer.* 2014;135(10):2404-2412.
20. Tahtali A, Hey C, Geissler C, et al. HPV Status and Overall Survival of Patients with Oropharyngeal Squamous Cell Carcinoma – A Retrospective Study of a German Head and Neck Cancer Center. *Anticancer Research.* 2013;33:3481-3486.
21. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9(1):e86023.
22. Zevallos JP, Mazul AL, Rodriguez N, et al. Previous tonsillectomy modifies odds of tonsil and base of tongue cancer. *Br J Cancer.* 2016;114(7):832-838.
23. Chaturvedi AK, Graubard BI, Broutian T, et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. *Cancer Res.* 2015;75(12):2468-2477.
24. Cook RL, Thompson EL, Kelso NE, et al. Sexual behaviors and other risk factors for oral human papillomavirus infections in young women. *Sex Transm Dis.* 2014;41(8):486-492.
25. Fu TC, Hughes JP, Feng Q, et al. Epidemiology of Human Papillomavirus Detected in the Oral Cavity and Fingernails of Mid-Adult Women. *Sex Transm Dis.* 2015;42(12):677-685.
26. Sivasithamparam J, Visk CA, Cohen EE, King AC. Modifiable risk behaviors in patients with head and neck cancer. *Cancer.* 2013;119(13):2419-2426.
27. Herrero R, Muñoz N, Franceschi S, et al. International case-control study of HPV and cancer of the oral cavity and pharynx. Paper presented at: The 18th International Papillomavirus Conference, 2000; Barcelona, Spain.
28. Fernandez Garrote L, Herrero R, Ortiz Reyes RM, et al. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. *British Journal of Cancer.* 2001;85(1):46-54.
29. Lissowska J, Pilarska A, Pilarski P, et al. Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev.* 2003;12(1):25-33.
30. National Center for Health Statistics. National Health Interview Survey, 2015. Public-use data file and documentation. 2016; https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.

31. CDC (Centers for Disease Control and Prevention). 2016 Behavioral Risk Factor Surveillance System Questionnaire. 2015; https://www.cdc.gov/brfss/questionnaires/index.htm.
32. Zhou J, Michaud DS, Langevin SM, McClean MD, Eliot M, Kelsey KT. Smokeless tobacco and risk of head and neck cancer: evidence from a case-control study in New England. *Int J Cancer.* 2013;132(8):1911-1917.
33. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF. Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. *Cancer Causes Control.* 2013;24(4):649-664.
34. Collins D. Pretesting survey instruments: an overview of cognitive methods. *Qual Life Res.* 2003;12(3):229-238.
35. Berthiller J, Straif K, Agudo A, et al. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-845.
36. Friesema IH, Veenstra MY, Zwietering PJ, Knottnerus JA, Garretsen HF, Lemmens PH. Measurement of lifetime alcohol intake: utility of a self-administered questionnaire. *Am J Epidemiol.* 2004;159(8):809-817.
37. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol.* 2010;39(1):166-181.
38. National Cancer Insitute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Oral Cavity and Pharynx Cancer. https://seer.cancer.gov/statfacts/html/oralcav.html. Accessed March 15, 2019.

SYNTHESIS

This dissertation sought to identify WTC-related and behavioral risk factors for HNC among WTC responders, with the overarching goal of developing a risk factor profile, which may help promote prevention and early detection of HNC in this population. We implemented three projects aimed to (1) develop and assess the reliability of a questionnaire designed to retrospectively reconstruct risk behaviors before, during, and after the WTC exposure period; (2) evaluate WTC-related and behavioral risk factors for HNC among WTC responders using a nested case-control approach; and (3) compare the distribution of risk factors for HNC subtypes among WTC responders using a case-case approach.

Overview of Findings

The first study involved thorough development and testing of a questionnaire that assessed important behavioral risk factors over the lifetime and specifically relative to the WTC response period. We demonstrated high agreement between smoking behavior assessed by our questionnaire and that assessed by WTCHP monitoring visit questionnaires prior to HNC diagnosis, which alleviates concerns about recall bias. However, we also found evidence of reporting bias, in that a small portion of former cigarette smokers did not report having previously smoked on our questionnaire, potentially due to changes in social norms related to smoking over the past decade. Since this did not occur significantly more for cases or controls, the resulting misclassification is likely nondifferential and would attenuate, rather than exaggerate, the effect of smoking observed during case-control analysis. Our results also suggest that some responders, particularly those in the protective services, may have underreported their alcohol consumption during their monitoring visits, underscoring the value of assessing this potentially sensitive information separately from the WTCHP clinic setting. In addition, we saw potential for a mode effect, because agreement for two smoking intensity measures was higher among participants who completed our survey by telephone as opposed to online. This finding highlights the importance of exploring the impact of survey mode in the other two studies.

The second part of this dissertation was a nested case-control study of HNC among WTCHP GRC members. We found that increased lifetime and post-WTC years of cigarette smoking and post-WTC number of sex partners were associated with increased estimated risk of HNC. The observed effect of lifetime smoking duration is consistent with existing literature linking tobacco smoking to HNC and adds to the growing body of research associating HNC with long duration of low-frequency smoking.[1,2] The strong effects observed for post-WTC smoking is consistent with a mediation hypothesis whereby PTSD following WTC exposure led to continued (or relapse to) smoking. The observance of number of sex partners (an established indicator of HPV infection risk[3-5]) as a risk factor in the post-WTC period also supports a mediation hypothesis. Taken together, these findings suggest that smoking cessation and HPV-prevention measures (e.g., risk reduction education, vaccination) may help reduce HNC risk in this population.

Although we saw no significant main effects of WTC exposures, those with protective services occupations had significantly greater odds of HNC than those in other occupations. This may reflect risk associated with job tasks specific to those in the protective services during the WTC efforts (e.g., search and rescue[6]) that were not wellcaptured by the WTC exposure measures we considered in this study, or other non-WTC-related occupational risk factors. We also found that arrival on 9/11 as opposed to later was associated with increased risk among those not in the protective services, while duration of work was inversely associated with HNC among those who never worked "on the pile," which suggests that WTC exposures, in relation to HNC risk, are complex and a function of multiple time, location, and task factors.

We did not expect to observe nonsignificant inverse associations with alcohol in our nested case-control analysis, but the results from our third study demonstrate that this likely reflected heterogeneous risk factor profiles among cases. Our case-case analysis found that cumulative alcohol consumption varied significantly by cancer site and was highest for the laryngeal cancer cases, who comprised only 17% of cases. This finding is consistent with other studies finding relatively weak or no association between alcohol consumption and oropharyngeal cancers, which instead tend to be HPV-associated and comprised the majority of our sample. We did not observe differences in the effects of smoking by cancer site, which suggests that smoking is an important risk factor for HNC regardless of tumor site.

We were surprised to find no difference in number of sex partners by cancer site for several reasons: our nested case-control study found a positive association between risk for HNC and post-WTC number of sex partners; the majority of cases in our sample had oropharyngeal cancer; and oropharyngeal cancers are strongly associated with both sexual activity and HPV infection in the general population. This may reflect underreporting of sexual behavior among those with oropharyngeal cancer in our population, but also suggests that the proportion of these cancers that are HPV-attributed may be less than in the general population. Future studies comparing the risk factor profiles for WTC-exposed and unexposed populations, as well as assessment of HPV tumor status among GRC members with HNC, may help shed light on this issue.

Limitations

The three studies presented for this dissertation share some limitations for consideration. In all three studies, small sample size limited our ability to conduct more refined analyses. In efforts to increase efficiency, we modeled cumulative smoking and drinking continuously in regression analyses; however, with this approach, we could not explore alternative relationships that may be observable through categorization of these variables, such as a minimum threshold effect. In addition, we could not asses ever-never status of certain behaviors (e.g., smokeless tobacco use) and occupational exposures due to small numbers.

As demonstrated by the results of our first study, there is potential for reporting bias and mode effects in studies two and three. However, we found no evidence of differential misclassification by disease status or, among cases, cancer site; thus, the likely impact is attenuation, rather than exaggeration, of effects. We also saw potential for a mode effect in the first study, but we did not find evidence of a significant mode effect in the case-control and case-case studies.

Selection bias is possible for all three studies, if persons who enrolled differ from those who were eligible but did not enroll. We alleviated some of this concern by demonstrating minimal differences between participants and non-participants with respect to demographics, WTC exposure measures, and cigarette smoking (as assessed by

WTCHP); however other differences may exist that we could not assess. In addition, self-selection into the broader WTCHP GRC limits our ability to generalize findings to WTC-exposed persons not enrolled in the GRC.

Implications

Our results contribute to development of a risk factor profile for WTC responders, which our findings suggest may be different from that of the general population, and support the need for continued monitoring of WTC-exposed persons. In these populations, the clinical level of suspicion prompting referral for HNC testing should be low, even for persons who do not fit the general population description of "high risk." For example, in the general population, clinicians would unlikely regard persons who never drank heavily or never smoked cigarettes at high levels as "high risk" for HNC; however, we encourage clinicians who treat WTC-exposed individuals to consider the possibility of HNC in such patients who might otherwise be deemed "low risk." We also recommend increased monitoring of risk behaviors, such as expanding WTCHP questionnaire modules to include:

- Additional detail about current and former tobacco use, specifically: assessment of frequency and duration of tobacco use before, during, and after the WTC response, accounting for periods of cessation; and, for persons with a WTC-certifiable health condition, assessment of tobacco use prior to diagnosis.
- Additional detail about current and former alcohol use, specifically: assessment of frequency and duration of alcohol consumption before, during, and after the WTC response; assessment of heavy alcohol consumption before, during, and after the

WTC response; and, for persons with a WTC-certifiable health condition, assessment of alcohol consumption prior to diagnosis.

- Assessment of HPV risk factors, specifically: assessment of number of sex partners before, during, and after the WTC response; and, for persons with a WTC-certifiable health condition, number of sex partners in the years prior to diagnosis.

In addition, there may be recall issue particular to WTCHP members who enroll after diagnosis of cancer or another WTC-certifiable condition. Standardization of data collection procedures, including question phrasing for interviewer-administered questionnaire, may help reduce potential for misclassification. Together, these recommendations may improve HNC detection and treatment outcomes in this population.

We further propose that smoking cessation and HPV risk reduction interventions may be beneficial for reducing HNC risk among GRC members. For tobacco use, this includes clinical assessment and referral for tobacco cessation treatment. For HPV risk reduction, this includes assessment of high-risk sexual behaviors, with referral as needed, education to increase awareness that HPV can cause HNC and inform responders about ways to reduce risk of infection, and vaccination (when indicated by age),

Future Research Directions

These recommendations may not only be applicable to GRC members. There were an estimated 500,000 people potentially exposed to WTC pollution. Some are enrolled in additional WTCHP cohorts that monitor New York City Fire Department

(FDNY) responders and people who lived, worked, or attended school or day care near the WTC site (New York City [NYC] Survivors). Research of risk factors for HNC should be conducted within the FDNY Responder and NYC Survivor cohorts, to assess whether risk factor profiles are similar to what we observed among GRC members. As well, pooled analyses of multiple studies could generate more precise effect estimates. Finally, future studies comparing the risk factor profiles for WTC-exposed and unexposed populations, as well as assessment of HPV biomarkers among WTC-exposed persons with HNC, may also help elucidate and explain observed differences between general population and WTC-exposed HNC risk factor profiles.

Conclusions

A diagnosis of HNC can be devastating, particularly for WTC responders, many of whom endure PTSD as a result of their experience.[7] Risk of treatment failure and death from these cancers is high, with five-year survival rates of less than 64%.[8] Many patients that do survive suffer from persistent symptoms even after treatment, including disfigurement, difficulty swallowing, sleep disturbances, pain, depression, and anxiety.[9] The number of HNC cases identified in the GRC has more than doubled since we closed enrollment to our study in 2016 (C. Dasaro, email communication, October 30, 2018), underscoring the importance of continued research into HNC among WTC-exposed populations.

Although we hope to never again see a disaster like 9/11, it is plausible that similar exposures could occur, for example, a building collapse following a natural disaster. This and other research of WTC-exposed populations underscores the importance of preventive measures (e.g., appropriate use of personal protective equipment) and long-term behavioral and medical monitoring of exposed persons.

REFERENCES

1. Berthiller J, Straif K, Agudo A, et al. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-845.
2. Lubin JH, Purdue M, Kelsey K, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol.* 2009;170(8):937-947.
3. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. *N Engl J Med.* 2007;356:1944-1956.
4. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9(1):e86023.
5. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol.* 2010;39(1):166-181.
6. Woskie SR, Kim H, Freund A, et al. World Trade Center disaster: assessment of responder occupations, work locations, and job tasks. *Am J Ind Med.* 2011;54(9):681-695.
7. Wisnivesky JP, Teitelbaum SL, Todd AC, et al. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. *Lancet.* 2011;378(9794):888-897.
8. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Statistics. https://seer.cancer.gov/statistics/summaries.html. Accessed Aug. 11, 2017.
9. Murphy BA, Deng J. Advances in Supportive Care for Late Effects of Head and Neck Cancer. *J Clin Oncol.* 2015;33(29):3314-3321.

BIBLIOGRAPHY