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RESEARCH ARTICLE

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Cancer incidence among boat-building workers exposed to styrene

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Background: A cancer incidence analysis was conducted on The National Institute for Occupational Safety and Health boat-builders cohort exposed to styrene, a possible carcinogen.

Methods: Standardized incidence ratios (SIR) and standardized rate ratios (SRR) were calculated using national and Washington State rates and a person-years analysis program.

Results: Among 3704 workers living in Washington State after 1991, when cancer registry case accrual began, 516 first primary diagnoses occurred through 2007. While overall cancer incidence was significantly reduced [SIR: 0.83 (0.76, 0.90)], internal comparisons suggest an association with exposure comparing high to low exposed person-time [SRR: 1.28 (1.05, 1.55)].

Conclusion: There is evidence of styrene exposure being linked to cancer incidence, which is notable since the cohort has not yet reached the median age of cancer diagnosis (65) in the United States.

KEYWORDS
cancer incidence, neoplasms, occupational exposure, styrene

1 | INTRODUCTION

The International Agency for Research on Cancer (IARC) classifies styrene in Group 2B, possibly carcinogenic to humans, and the major human metabolite, styrene-7,8-oxide, in Group 2A, probably carcinogenic to humans.[1,2]. In addition, styrene and styrene oxide have been classified as reasonably anticipated to be human carcinogens by the Report on Carcinogens.[3]

This study hopes to add to the current research on the association of occupational exposure to styrene and cancer, using the National Institute for Occupational Safety and Health (NIOSH) boat-building cohort that includes 5203 workers who were exposed to styrene at some time between 1959 and 1993 at either of two plants in Washington State. Previous studies of the effects of occupational styrene exposure have focused on its effects on the risk of lymphohematopoietic cancers, and results have been mixed. For example, Hodgson and Jones,[4] Ott et al,[5] and Kogevinas et al[6] found an excess of lymphoma in their respective cohorts, though the excess was not associated with varying levels of exposure, such as duration or cumulative exposure. In addition, Delzell et al[7] did see an elevation in leukemias as well as an associated exposure response with cumulative styrene exposure. In contrast, Collins et al[8] found no elevation in lymphoma in their cohort of over 15 000 US workers in reinforced plastic facilities.

We recently completed a mortality study of this cohort,[9] but did not find an excess of leukemia; however, this was based on only six deaths. On the other hand, we did see evidence of an excess in lung cancer [SMR: 1.26 (0.95, 1.56)] as well as an excess of ovarian cancer [SMR: 3.08 (1.00, 7.19)].

While cohort mortality studies have been a mainstay of occupational cancer epidemiology for decades, for cancer sites with low mortality, cancer mortality studies may not be the best way to investigate the relation between exposure to a potential carcinogen and the risk of cancer.[10] Furthermore, since by definition excess risk due to occupational exposures cannot be determined until after a majority of the cohort has died, mortality studies do not provide the opportunity to notify cohort members of risks in a timely manner and to encourage them to complete cancer screenings.[11–13]

Therefore, for this analysis, we conducted a cancer incidence study in the NIOSH boat-building cohort, using data from the Washington State Cancer Registry because the majority of the workers in the cohort were still residing in Washington State. We evaluated risk of cancer incidence, for all organ sites, including leukemia and lymphoma, among men and women.

2 | METHODS

Details about cohort enumeration and mortality statistics through 2011 are presented elsewhere.[9] Briefly, the study cohort includes everyone with complete demographic information (name, birthdate, dates employed) employed at either of the two study plants in Washington State for at least one day between 1959 and 1978. Demographics and work histories (but not job titles, which were missing from many records) were abstracted from personnel records in 1978. When personnel and other records were obtained in 1978, there were 772 active workers and their work history records are incomplete if they continued working after 1978. We were unable to update work histories of the employees active in 1978 since company records were incomplete or unavailable after 1993, the year both plants had ceased production (plant A in 1993, plant B in 1989).

To ascertain vital status and causes of death, worker data were linked to the Social Security Administration and the National Death Index (NDI). Causes of death after 1979 were obtained from NDI Plus. For deaths occurring prior to 1979, death certificates were obtained from state vital statistics offices and coded by a certified nosologist to the International Classification of Diseases revision in effect at the time of death.

2.1 | Residential history

Cancer diagnosis databases are maintained at a state level. For this particular study, we only linked worker data to the Washington State Cancer Registry, which identifies those diagnosed with cancer while living in Washington State. Full ascertainment for Washington did not begin until 1991. As a result, for each worker, we needed full residential history to identify when and where they lived to determine if a potential cancer diagnosis would be observed.

Available address information for each worker was used to estimate dates when the workers first entered and first left the catchment area, defined as residing in Washington State between 1991 and 2007. Workers who died, were lost to follow up, or moved out of state before 1991 would never have been in the catchment area. Multiple sources of address information were considered. Some addresses during the period of employment were available from plant personnel records obtained by NIOSH in 1978. Various tracing efforts included the Internal Revenue Service, Post Office, credit services, and LexisNexis® (a private vendor of residential information) with LexisNexis® providing the most complete residential detail for this study.

Since only changes in the state of residence were relevant, these sources of address information were combined to create a residence history for each worker. State of residence was estimated for gaps (ie, time periods with no known address information) by dividing the gap at the midpoint and assigning the earlier state to the first half of the gap and the later state to the second half of the gap . For a given follow-up year, the worker was considered to be in the registry catchment if assigned to be living in Washington State in that year.

Workers never known to have lived in Washington State after 1991 (based on all available address information) were excluded from the cancer incidence analyses. Workers who left the state or died prior to the study end date only contributed person-years at risk (PYAR) until the date they were known to have migrated or died. Although some of these workers may have returned to Washington State later, the analysis only considered the initial risk period. Residency was estimated based on a set of rules independent of case status. For example, if a person was estimated to not be living in Washington but had then appeared in the Washington cancer registry, then this case would not have been included, to avoid bias. For this particular cohort, this was never an issue.

2.2 | Cancer registries

All workers were matched to the Washington State Cancer Registry, with complete ascertainment beginning in 1991. The registry provided matching through December 31, 2007. From the cancer registry we received: date of diagnosis and International Classification of Diseases for Oncology Third Edition (ICD-O-3) codes for primary site, laterality, morphology (histology and behavior), and stage. Incident cases were defined as all primary invasive cancers and in situ bladder cancers occurring in Washington State between 1991 and 2007; these were classified into 12 major and 41 minor cancer incidence groupings. Diagnosis dates were assigned as June 30 of the diagnosis year if only the year was known, and on the 15th of the diagnosis month if only the month and year were known.

2.3 | Exposure assessment

Detailed work history records, including begin date, end date, and department, were available for all workers. Department-specific exposure levels, based on personal and area samples collected in 1978, were used to calculate estimated potential styrene exposure. Workers ever in the fibrous glass (Company A, mean styrene time-weighted average 42.5 ppm, range 12-85 ppm) or lamination (Company B, mean styrene time-weighted average ppm 71.7 ppm, range 10-183 ppm) departments were considered potentially high.[14] All other workers, generally those primarily in boat assembling, administrate and general plant-wide departments, were considered only low exposed. Job-title-specific exposure was not available.

Due to limited job-title exposure data and lack of complete employment information for those currently employed during data collection, we chose to use the simple exposure definition of ever/never worked in a high styrene exposed department, which was used in the previous analyses of this cohort.[15,16]

2.4 | Life-table methods

Standardized incidence ratios (SIRs) obtained from a life-table analysis program (LTAS.NET)[17] were used to compare the cancer rates for 41

cancer groupings among all workers to a referent population. For this analysis, the numerator was based on first primary invasive cancers among eligible cohort members. For each worker, the risk begin date was the later of the date first employed and January 1, 1991 (the date the Washington Cancer Registry began). The risk end date was the earliest of the date of diagnosis (for cases), the date last observed (for workers lost to follow-up), the date of death (for deceased workers), the date the worker left Washington State, and the study end date (for workers alive and cancer free on December 31, 2007 and not known to have left Washington State). Person-time at risk was stratified according to age (in 5-year categories), calendar year (in 5-year categories), gender and race, and strata specific cancer incidence rates were obtained to calculate expected numbers of cases. The SIR was defined as the ratio of the observed to the expected numbers of cases and 95% CIs were estimated under the assumption of a Poisson distribution. Based on where the plants were located, Caucasian race was assumed when race was unknown ($n = 6$) in all analyses. Analyses of the first primary invasive cancer (overall and site-specific) used cancer incidence rates for a referent population based on Surveillance, Epidemiology, and End Results (SEER) program data on cancer incidence (1976-2009); these rates were adjusted for cancer prevalence using methods described by Merrill, to eliminate prevalent (non-first-primary) cancers.[18]

Standardized rate ratio (SRR) analyses internally comparing the incidence experience by exposure levels of the cohort were also performed. For each outcome, the person-time was further stratified by ever/never worked in a high styrene exposed department as previously detailed. SRR analyses were repeated but restricted to those with at least one year of employment at one of the two plants since, as our previous analysis showed, workers employed less than 1 year had a different risk profile, with excess mortality from alcoholism, accidents and homicides. In all analyses, 95% confidence intervals (CIs) were calculated.

2.5 | Human subjects review

This study (HSRB-08-DSHEFS-02XP) has been approved by the NIOSH Institutional Review Board. As a records study, it was exempted from informed consent requirements. It has also received approval from the research approval process for the Washington State cancer registry.

3 | RESULTS

3.1 | Residential history

Of the 5203 workers in this cohort, only 4654 were known to be alive after the Washington State cancer registry was in operation beginning in 1991. There were 510 workers who had died and an additional 39 lost to follow-up prior to 1991.

Address information from at least one of the sources considered was available for all workers known to be alive after 1991 with the most detailed information provided by LexisNexis®. LexisNexis® had addresses for a majority ($n = 4334$) of the eligible workers (median three addresses per worker, range 1-20). Address years provided by LexisNexis® ranged from 1946 to 2012, but only approximately 16% were in 1991 or earlier. Considering all sources of address information, state of residence had to be assumed for 14% of the person-years at risk from 1991 to 2007.

Based on the residential history constructed for each worker, an additional 950 workers were excluded due to having been believed to have moved out of Washington State prior to 1991. As a result, there were 3704 eligible workers for this cancer incidence study.

There were 892 deceased workers for whom we have addresses. Of these, two were assigned as living outside of Washington, based on our algorithm, although they had died in Washington State based on death certificate records. So the algorithm worked well with an error rate of only 0.2%.

3.2 | Case ascertainment—First primary cancer

From the Washington State Cancer Registry we identified 516 invasive cancer diagnoses through 2007 among 3704 eligible workers. Diagnosis dates were based only on year for two matches and complete for 514 matches. All cases were diagnosed after the workers began employment at the facilities (at least 14.6 years after employment began, mean 33.7 years, maximum 52.0 years).

We censored PYAR for workers who left the catchment prior to the study end date. Some of these migrating workers returned to the catchment at later dates ($n = 60$), but the analysis only considered the initial risk period and therefore, ignored 39 matched diagnoses that occurred after these workers first left the catchment.

3.3 | Life-table analyses

There were 772 workers currently employed during data collection in 1978, and their work history after 1978 was therefore missing. Of the 772 workers currently employed, 152 were dropped due to the catchment criteria. Of the 620 who were retained for the analyses, 225 were classified as ever worked in a high styrene exposed department and the remaining 395 were classified as having never worked in a high styrene exposed department.

Characteristics of cancer cases and non-cases are presented in Table 1. For the analysis of first primary invasive cancer incidence, 516 cases were observed among 3704 workers contributing 63 117 person-years at risk. The cohort for this study was relatively young, with a median age of 44 at the beginning of follow-up in 1991. Table 2 presents SIRs and SRRs for various cancer outcomes. Results were restricted to outcomes with at least three incident cases to allow for an adequate number of cases for the SRR analysis as well as to protect worker confidentiality. Compared to the referent population, overall cancer incidence was significantly reduced [SIR: 0.83 (0.76, 0.97)]. A slight elevation was observed for incident cancers of trachea, bronchus, and lung [SIR: 1.11 (0.89, 1.37)], with a borderline significant rate among workers with potential high exposure [SIR: 1.42 (1.00, 1.95)]. Four women with potential high styrene exposure (and none

TABLE 1 Characteristics of eligible workers, by case status, as of December 31, 2007 NIOSH Styrene Cohort: Composition of the entire cohort and subcohorts as of December 31, 2011

Characteristic	Entire in-state cohort	Individuals with cancer	Cancer-free individuals
Race/gender (%)[b]			
Females, nonCaucasian	36 (1%)		
Females, Caucasian	503 (14%)		
Males, nonCaucasian	181 (5%)		
Males, Caucasian	2984 (81%)		
Total	3704		
Median age at first employment (interquartile range)	23 (20, 30)	29 (22, 39)	23 (19, 28)
Median age on January 1, 1991 (interquartile range)	44 (39, 51)	49 (43, 61)	43 (39, 49)
Median years of employment (interquartile range)	0.47 (0.13, 1.57)	0.60 (0.15, 2.86)	0.45 (0.13, 1.45)
Mean years of employment (standard deviation (s))	1.69 (3.16)	2.52 (4.17)	1.56 (2.94)
Workers employed ≥1 years (%)	1264 (34%)	209 (41%)	1055 (33%)
Person years at risk	63 117	5974	57 143
Never worked in high styrene exposed dept.	35 937	3445	32 493
Ever worked in high styrene exposed dept.	27 180	2529	24 650

[a]A total of 1499 cohort members, not resident in Washington State after 1991 when the registry began accruing cases, were excluded from the incidence study.
[b]"Alive" includes persons lost to follow-up before the National Death Index was initiated.

with only low exposure) were diagnosed with ovarian cancer [SIR 2.26 (0.62, 5.78)].

While overall cancer incidence were generally reduced when compared to national rates, internal comparisons suggest an association of cancer with styrene exposure. SRRs comparing ever high exposed to only low exposed person-time were generally elevated with rates of all cancers of ever high exposed being significantly elevated compared to low exposed [SRR 1.28 (1.05, 1.55)]. In addition, SRR estimates generally remained unchanged after restricting to workers with more than a year of employment, with the exception of lung cancer. However, the precision in these estimates decreased substantially due to dropping almost 75% of the cohort. Lung cancer, on the other hand, was no longer elevated after this restriction and actually suggested a negative association with styrene exposure.

4 | DISCUSSION

Cancer is a major public health problem in the United States with annual incidence for all sites combined of 435.23/100 000 (1.67 million diagnoses estimated for 2014) and annual mortality of 161.30/100 000 (585 720 deaths estimated for 2014).[19] Because many cancers have high survivability, incidence may be a better metric than mortality,[10] so we decided to analyze cancer incidence in the styrene cohort. We included all cancers in an effort to determine whether elevated mortality for lung and ovarian cancer, observed in our mortality study[9] was consistent with incident cancer diagnoses. The original motivation to study this cohort was to test the hypothesis that leukemia and lymphoma might be associated with exposure to styrene.[4,5,16] However, we did not find a notable excess of lymphatic and hematopoietic cancers.

We did not find excess incidence for most cancers other than respiratory and ovarian cancers (Table 2) when compared to external referent populations, suggestive of a potential healthy worker effect. Also, the sub-cohort in this study is still very young. Median age in 1991 was 44 (range 39-51) and an additional 16 years of follow up still does not bring them to 65, the median age of cancer diagnosis in the United States.[20] However, internal comparisons did show that those with potentially high exposure to styrene had higher incidence to all cancers considered than those with only low exposures.

Other recent studies of cancer in styrene-exposed cohorts have had mixed results. Coggon et al[21] did not find excess lymphohematopoietic cancer in a British cohort, either in their mortality or incidence analyses, but they did find excess lung cancer. In contrast, several other epidemiologic studies have not found an association with styrene exposure and lung cancer risk.[6,22,23] A US study found neither excess lymphohematopoietic nor lung cancer.[8] Additionally,[24] found a possible association between styrene exposure and renal cell carcinoma. We did not find a kidney cancer excess.

IARC has not evaluated styrene carcinogenicity since 2002. However, the National Toxicology Program[3] states that styrene is "reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans." The report also lists genotoxicity as a mechanism for all cancers based on blood samples from styrene-exposed workers,[25] as well as cytotoxic effects in the lung based on an inhalation study in mice.[26] However, the cytotoxic effects in the lungs of mice finding was thought to be species dependent since other studies found no evidence of toxicity in the lungs of rats also exposed to styrene.

TABLE 2 Cancer incidence using US (SEER) rates and WA state rates, for cancer sites with >3 diagnoses

	Full cohort		Low exposed		High exposed		High vs low SRR	
	Obs	US SIR (95%CI)	Obs	US SIR (95%CI)	Obs	US SIR (95%CI)	SRR (95%CI)	Restricted[a] SRR (95%CI)
All cancer	516	0.89 (0.81, 0.97)	310	0.82 (0.73, 0.92)	206	1.01 (0.88, 1.16)	1.28 (1.05, 1.55)	1.24 (0.87, 1.77)
Buccal and pharyngeal cancer	11	0.61 (0.31, 1.10)	4	0.35 (0.10, 0.90)	7	1.06 (0.43, 2.19)	3.83 (1.07, 13.7)	3.53 (0.47, 26.48)
Colon and rectum cancer	47	0.84 (0.62, 1.12)	32	0.86 (0.59, 1.22)	15	0.79 (0.44, 1.30)	1.07 (0.51, 2.23)	1.03 (0.37, 2.85)
Other digestive organ cancers and peritoneum	46	0.96 (0.70, 1.28)	29	0.93 (0.62, 1.34)	17	1.01 (0.59, 1.62)	1.27 (0.66, 2.44)	2.00 (0.40, 9.95)
Respiratory and intrathoracic organ cancers	90	1.04 (0.83, 1.28)	53	0.92 (0.69, 1.20)	37	1.27 (0.90, 1.76)	1.33 (0.82, 2.14)	0.64 (0.32, 1.28)
Trachea, bronchus and lung cancer	87	1.11 (0.89, 1.37)	50	0.96 (0.71, 1.27)	37	1.42 (1.00, 1.95)	1.41 (0.87, 2.29)	0.66 (0.33, 1.34)
Breast cancer	21	0.81 (0.50, 1.23)	6	0.67 (0.25, 1.46)	15	0.88 (0.49, 1.45)	1.38 (0.53, 3.60)	1.41 (0.29, 6.93)
Female genital organ cancers	8	0.83 (0.36, 1.63)	NRb	0.31 (0.01, 1.75)	NRb	1.08 (0.43, 2.23)	2.70 (0.33, 22.0)	1.65 (0.19, 14.15)
Ovarian Cancer	4	1.52 (0.41, 3.89)	0	0.00 (0.00, 4.27)	4	2.26 (0.62, 5.78)	–	–
Prostate cancer	140	0.82 (0.69, 0.97)	89	0.74 (0.60, 0.91)	51	1.02 (0.76, 1.34)	1.27 (0.87, 1.87)	1.12 (0.61, 2.03)
Urinary organ cancers	51	1.00 (0.75, 1.32)	32	0.93 (0.63, 1.31)	19	1.17 (0.70, 1.82)	1.25 (0.68, 2.29)	2.00 (0.83, 4.78)
Thyroid and other endocrine organ cancers	5	0.79 (0.26, 1.84)	NR[b]	1.17 (0.32, 2.99)	NR[b]	0.34 (0.01, 1.91)	0.44 (0.05, 3.95)	–
Other solid cancers	32	0.75 (0.51, 1.05)	17	0.63 (0.37, 1.02)	15	0.93 (0.52, 1.54)	1.43 (0.70, 2.91)	0.43 (0.09, 2.12)
Lymphatic and hematopoietic organ cancers	47	1.03 (0.77, 1.35)	35	1.05 (0.73, 1.46)	18	0.99 (0.59, 1.57)	1.16 (0.63, 2.14)	1.92 (0.73, 5.04)
Ill specified and residual cancers	16	0.79 (0.38, 1.45)	6	0.71 (0.26, 1.54)	4	0.96 (0.26, 2.45)	1.19 (0.33, 4.35)	–

[a]Restricted to person-time with more than 1 year of employment.
[b]Numbers in small cells not reported to protect worker identity.

Washington State Cancer Registry only (71% of the mortality cohort members who died through 2007 died in Washington State). Many issues associated with trying to achieve complete ascertainment of cancer diagnoses have been discussed.[27] Cancer diagnoses outside of Washington State or before the state registry began operation in 1991 were not available for this analysis. Consequently, person-time for individuals not living in the catchment was excluded when estimating expected numbers of cases. This calculation, however, relied on available residential history information, and the state of residence had to be assumed for 14% of the potential person-years at risk.

In addition, the SEER rates are intended to apply to the entire US population, not just the population of the SEER catchment.[19] SEER Program data include cancer incidence and survival from population-based cancer registries covering approximately 28 percent of the US population through 2006, and the population of the participating registries' catchment areas is considered a representative sample of the US population.[28] If the SEER rates actually overestimate national incidence, that would result in overestimation of the expected number of cases and underestimation of the SIRs. Even if the SEER rates accurately reflect the entire US population, the healthy worker effect has been observed in cancer incidence studies, especially among men. The healthy worker survivor effect has been shown to attenuate exposure-response relations Stayner et al[29] but the effect may be diminished with increasing follow-up.

Another limitation of this study is the simple ever/never exposure metric used. Due to limited employment data, a more refined cumulative exposure metric was not supported. In addition, in the sub-cohort of this study, 620 workers were employed at the time of data collection and therefore, their work history after 1978 is missing. Of these 620 workers, 395 were classified as having never worked in a high styrene exposed department and it is possible that some of these 395 individuals may have been misclassified if they later did go on to work in a high exposed department.

Finally, there is limited available data of other confounding exposures for this cohort, including smoking. This is especially true for the lung cancer results, which show a slight elevation when compared to the referent population; however, this elevation could not be linked to styrene exposure. The SRR analysis actually suggest a negative relationship with exposure when comparing high vs. low person time, when restricted to person time with more than one year of employment.

Furthermore, as Table 1 shows, those diagnosed with cancers tended to have been first employed by the facilities later in life, with the upper quartile as high as 39. We unfortunately do not have information on previous employment and any associated hazards.

In conclusion, while this cohort is still young for cancer diagnosis, we did see evidence of high styrene exposure contributing to an overall increased cancer diagnosis. Future follow-up may provide more insight.

AUTHORS' CONTRIBUTIONS

Avima Ruder obtained records and data required in updating the cohort, drafted first draft of the manuscript. Stephen Bertke performed all statistical analyses, contributed to interpretation of results, drafted all subsequent versions of manuscript, and addressed all reviewer comments during peer review

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ETHICS APPROVAL AND IN FORMED CONSENT

This research was approved by the Institutional Review Board of the National Institute for Occupational Safety and Health (NIOSH).

DISCLOSURE (AUTHOR)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. The use of trade names is for identification only and does not imply endorsement by the US Department of Health and Human Services or by the Centers for Disease Control and Prevention.

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