The Wilmington Childhood Cancer Study

An Epidemiologic Investigation of
Childhood Cancer from 1990–2000

EXECUTIVE SUMMARY

MARCH 2021

This is the executive summary of the
Wilmington Childhood Cancer Study.

The final report and other information
about the study are available on the
Massachusetts Department of Public Health website.

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STUDY HIGHLIGHTS

- Elevated rates and an unusual pattern of childhood cancer in the town of Wilmington during the 1990s led to the undertaking of a broad environmental case-control study by the Massachusetts Department of Public Health (DPH).

- DPH interviewed each study participant and matched control to collect detailed information on residential history and major cancer risk factors including maternal health behaviors; family and child medical histories; and occupational or household exposures such as pesticides and solvents.

- In 2003, a carcinogenic compound, *n*-nitrosodimethylamine (NDMA), was found in the groundwater supplying part of the town's public drinking water. This discovery prompted a comprehensive water modeling effort to reconstruct historical concentrations of NDMA at the residences of each study participant for each month between 1974 and 2000. An additional carcinogenic contaminant, trichloroethylene (TCE), was also present in the water supply during part of the study period and the report details analyses related to both compounds.

- Despite limitations, including a small sample size and modeled exposure estimates, study results show an association between childhood cancer and prenatal exposure to NDMA, or NDMA and TCE. This association is observed consistently in a series of analyses and the results are statistically significant with respect to the subset of leukemia or lymphoma diagnoses. These associations exhibit a dose-response trend in which higher estimated exposures result in higher odds of cancer and the associations remained positive even after adjustment for other known risk factors.

- Childhood cancer incidence returned to expected rates beginning in 2001.

The Massachusetts Department of Public Health (MDPH) was asked to investigate a suspected cluster of childhood cancer in Wilmington, MA. Local residents and the local board of health were concerned about what appeared to be an unusual number of childhood cancer cases during the 1990s. After a review of cancer incidence data for the years in question, the MDPH confirmed the presence of an unusual pattern of cancer among children and adolescents (aged ≤ 19 years) within two census tracts located in the southern and western portions of the town. Consequently, the MDPH initiated an epidemiologic case-control study to investigate factors that may be associated with cancer development in the town of Wilmington among children and adolescents diagnosed between 1990 and 2000.

Shortly after initiation of the study, a specific drinking water contaminant and carcinogen, *n*-nitrosodimethylamine (NDMA), was detected in an aquifer providing part of the Wilmington drinking water supply. The contamination occurred as a result of activities at a chemical manufacturing facility operating in the south-eastern corner of town from 1953–1986. The site, known as the Olin Chemical site, was later designated a Superfund National Priorities List site by the US Environmental Protection Agency. Potential exposure to NDMA and to another carcinogenic drinking water contaminant known to have been present in the Wilmington public drinking water distribution system in the 1970s and 1980s, trichloroethylene (TCE), became the focus of this investigation.

METHODS

Cases of childhood and adolescent cancer occurring in Wilmington, MA, during the period of concern were identified through the MDPH Massachusetts Cancer Registry and through Massachusetts hospital discharge records. Eligible cases were those diagnosed with a first primary cancer prior to their 20th birthday, with a diagnosis date between January 1, 1990 and December 31, 2000, and who were residents of Wilmington at the time of diagnosis. One case of melanoma that was otherwise eligible, was excluded since sunlight exposure is the major risk factor for that cancer type, making the case unlikely to be relevant to this environmental investigation.

Eighteen out of twenty-one eligible children and adolescents were enrolled in the study. In addition, seventy-four control children and adolescents (approximately four controls per case matched on age and sex) were enrolled in the study. Controls were randomly selected from public school rosters and Wilmington high school yearbooks and were required to have lived in Wilmington during the same month and year of their matched case's cancer diagnosis. The parents of all study participants completed a comprehensive structured interview to collect residential histories as well as risk factor information such as maternal alcohol use, smoking status, and reproductive history; child/adolescent's medical history; child/adolescent's daycare, school, camp, and recreational history for specific locations in Wilmington; occupational history for each child or adolescent (if applicable) and parent; and potential household exposures such as pesticides and solvents.

Utilizing residential history information collected during participant interviews, MDPH estimated exposure to NDMA for the period 1974–2000 using sophisticated computer models to replicate historical groundwater flow, transport of NDMA through the groundwater, and distribution of NDMA throughout the Wilmington public drinking water system. TCE was modeled over the period 1981–2000. Modeling of TCE concentrations prior to 1981 was not possible due to the absence of earlier sampling data along with the lack of a known source within the aquifer. Each contaminant was evaluated for an association with the odds of childhood/adolescent cancer based on exposure during two etiologic periods: the maternal exposure period defined as the year prior to the child/adolescent's birth (representing *in-utero* exposure) and the childhood exposure period encompassing all of childhood/adolescence from the month of birth to the date of diagnosis for each case and their matched control.

Modeled concentrations of NDMA and TCE in the water at each residential address were used as a surrogate for potential exposure. The estimated average of all non-zero monthly concentrations of NDMA was used as the measure of exposure to NDMA. The estimated average of all non-zero monthly concentrations of TCE was used as the measure of exposure to TCE. Analyses of NDMA and TCE exposure were conducted as dichotomous (ever/never) and as categorical (zero/low/high) where the division between low and high was based on the median average non-zero monthly concentration. Participants were asked about their primary drinking water source for each residence and analyses were also conducted to evaluate potential exposure while accounting for bottled water usage during the maternal exposure period.

Analyses of risk factors were conducted among all study participants combined (the All Cancers group) and separately for those diagnosed only with leukemia or lymphoma and their matched controls (the Leukemia/Lymphoma subgroup). The leukemia and lymphoma cases were analyzed together because there is some evidence that these cancer types may share a more similar etiology compared to all types of cancer combined.

RESULTS

Exposure Concentrations

For NDMA exposure in the All Cancers group, fifty percent (50%) of case mothers are estimated to have had NDMA present in their tap water during at least one month in the year prior to their child's birth compared to 34% of control mothers. The median non-zero monthly concentration estimated at the tap of case mothers is 52.2 ng/L compared to 46.8 ng/L for control mothers. The likelihood of having had any NDMA in residential tap water during childhood was similar for cases and controls (78% vs. 84%). Estimated median non-zero concentrations during the childhood period were also higher for cases compared to controls (51 ng/L versus 39 ng/L). Similar results are seen in the Leukemia/Lymphoma subgroup for both maternal and childhood NDMA exposure.

For TCE exposure in the All Cancers group, mothers of cases were slightly more likely to have had any TCE in their residential tap water compared to mothers of controls (31% compared to 25%), but median concentrations were similar between the two groups. The inverse is true for the childhood exposure period with controls being slightly more likely to have had at least one month with TCE estimated to be present in their tap water (53% of controls compared to 46% of cases). However, estimated median non-zero concentrations during the childhood period were approximately twice as high for cases compared to controls (5.2 μg/L versus 2.1 μg/L). Similar results are seen in the Leukemia/Lymphoma subgroup for both maternal and childhood NDMA exposure.

When joint exposures were evaluated for the maternal exposure period, it was observed that no participants were exposed to TCE alone and that 31% of cases and 25% of controls were estimated to have been exposed to both contaminants (among the 73 participants with modeled concentrations of both NDMA and TCE). A small, but statistically significant, correlation exists between the two contaminants in residential drinking water in this study, driven by the large number of participants with estimated zero exposure to both compounds.

Associations between NDMA in Drinking Water and Childhood Cancer

When evaluating maternal/*in-utero* exposure, the odds of childhood/adolescent cancer (all cancers and leukemia/lymphoma) were higher for children/adolescents whose mothers ever lived in a home estimated to have NDMA-contaminated drinking water during the year prior to birth, but these results did not reach statistical significance. A positive trend in the odds of cancer was also observed with increasing average estimated NDMA concentrations in maternal drinking water from zero to low to high for all cancers (ORs = 1.0, 1.3, 3.0) and for leukemia/lymphoma (ORs = 1.0, 1.3, 5.0). Tests of trend for these analyses resulted in a p-value of 0.12 for the All Cancers analysis and a p-value of 0.06 for the Leukemia/Lymphoma subgroup analysis. In the Leukemia/Lymphoma sub-analysis, the odds ratio of 5.0 was statistically significant for the high concentration group compared to the zero exposure group. The odds ratio of 3.0 for the high category of the All Cancers analysis was of marginal statistical significance (p = 0.09).

> An **odds ratio (OR)** is a measure of association between a health outcome and an exposure or risk factor. In general, an odds ratio is calculated as the odds of an exposed population developing a particular health outcome compared to the odds of an equivalent but *un*exposed population developing the health outcome.
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> - An OR of 1.0 means that exposure is not related to the outcome.
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> - An OR greater than 1.0 means that exposure has a positive association with the outcome
>
> - An OR less than 1.0 means exposure has a negative association with the outcome.
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> **Example:** *An odds ratio of 2.5 means that the odds of an outcome occurring with exposure is 2.5 times higher than if there were no exposure.*

In contrast to the results for maternal NDMA concentrations in drinking water, when evaluating concentrations estimated to have been present in residential drinking water during childhood/ adolescence, there was no evidence of a positive association between NDMA in drinking water with development of any cancer, including development of leukemia or lymphoma.

Associations between TCE in Drinking Water and Childhood Cancer

When evaluating maternal exposure to TCE, the odds of childhood/adolescent cancer (all cancers and leukemia/lymphoma) were higher for children/adolescents whose mothers ever lived in a home estimated to have TCE-contaminated drinking water during the year prior to birth, but these results do not reach statistical significance and the confidence intervals are very wide. A similar result was observed in the Leukemia/Lymphoma subgroup analysis. When evaluating childhood/adolescent TCE concentration estimates, there was no evidence of a positive association with development of cancer.

Other Considerations

When those reporting that they primarily drank bottled water were assigned zero exposure, associations between NDMA and childhood/adolescent cancer were no longer observed. However, when bottled water usage was accounted for in exposure assignments by decreasing estimated concentrations to 49% of modeled values, associations between NDMA and childhood/adolescent cancer were strengthened (though no longer in a dose-responsive fashion). For TCE, accounting for bottled water usage had less of an apparent effect.

The effect of possible confounding on the associations between childhood/adolescent cancer and exposure to NDMA and TCE was evaluated for each of eleven individual covariates: 1) oxygen given after birth, 2) incubator use after birth, 3) low birth weight, 4) adverse birth event, 5) prenatal ultrasound, 6) antihistamine use by the child/adolescent, 7) metals, alloys, or solder exposure, 8) plastics, synthetics, or resins exposure, 9) exhaust fume exposure, 10) herbicide exposure, and 11) maternal occupational exposure to ionizing radiation. These variables were selected for evaluation because they were found to have elevated odds ratios and *p*-values that were <0.20 for the association with all cancers or with leukemia/lymphoma, meaning that they had a reasonable potential to be confounders in the main exposure-outcome evaluation. In all adjusted models, potential exposure to NDMA and to TCE in maternal drinking water remained positively associated with childhood/adolescent cancer.

CONFIDENCE INTERVALS, *P*-VALUES, AND STATISTICAL SIGNIFICANCE

While an odds ratio (OR) provides a point estimate of the association between a risk factor and a health outcome, other tools are used to understand the reliability or precision of that estimate.

A **confidence interval (CI)** measures how precise the odds ratio is and provides a range of values within which the point estimate will fall 95% of the time given an unbiased sample and analysis. A CI that includes 1.0 means that the association is not statistically significant and may be due to chance, even if the OR estimate is much higher than 1.0. If the CI excludes 1.0, then the association can be considered statistically significant. A wide confidence interval that excludes 1.0 indicates that the association is statistically significant, but that the precise strength of the association is not clear.

A ***p*-value** is a related measure, which describes the statistical significance of an odds ratio or other effect estimate based on a pre-defined confidence threshold. A threshold of 0.05 (or 95% confidence) is generally applied. The larger a *p*-value, the less precise the OR is. However, importantly, a large *p*-value does not mean that the result is invalid. It may indicate that insufficient information is available to adequately evaluate the result, commonly due to small sample sizes.

DISCUSSION

The objective of this study was to obtain an explanation for the pattern of childhood cancer in Wilmington, MA between 1990 and 2000. Specifically, childhood/adolescent cancer rates were higher than would be expected and appeared to occur more frequently in certain areas of the town. The study was maximally designed to consider available risk factor data, given the relatively small number (from a statistical perspective) of children and adolescents with cancer, by using multiple controls, sophisticated exposure modeling, and detailed personal interviews. This study faced several challenges including a small sample size, a retrospective exposure assessment, and a retrospective ascertainment of additional risk factors. Nevertheless, strong positive associations were observed between contaminants in maternal residential drinking water and childhood/adolescent cancer.

The most compelling results include statistically significantly higher odds of a leukemia or lymphoma diagnosis among children or adolescents whose mothers lived in homes with the highest estimated *n*-nitrosodimethylamine (NDMA) concentrations in drinking water compared to children or adolescents whose mothers were estimated to have had no NDMA exposure during the year before their child's birth (OR = 5.0; 95% CI: 1.0–24). The odds of any cancer diagnosis were also elevated among this group, but with only marginal statistical significance (OR = 3.0; 95% CI: 0.8–11); because leukemia and lymphoma diagnoses made up 60% of the 18 cases in this study, the results of the All Cancers analysis are largely driven by the strong association observed with leukemia/lymphoma. Both associations displayed a dose-response trend, and the trend for the Leukemia/Lymphoma subgroup had a marginally significant *p*-value of 0.06. Estimated concentrations of trichloroethylene (TCE) in maternal drinking water were also positively associated with the odds of any cancer diagnosis, but results were not statistically significant, a dose-response effect was not observed, and the small number of participants with available estimated TCE concentrations prevented deeper analysis of the Leukemia/Lymphoma subgroup.

Assessing the effects of each contaminant in a multivariate model, while not wholly appropriate due to their correlated nature, nevertheless resulted in continued positive associations with childhood/adolescent cancer for both the All Cancers group and the Leukemia/Lymphoma subgroup. Such results may suggest independent associations of each contaminant with childhood/adolescent cancer in this population; however, the lack of a sample only exposed to TCE and the very small number of those only exposed to NDMA severely limits the ability to evaluate independent effects.

There is ample evidence in the published literature on the plausibility of NDMA causing cancer and it is considered a probable human carcinogen by both the US EPA and the International Agency for Research on Cancer (IARC) (IARC 1978, 1987; US EPA 2017). In animal studies, NDMA has been shown to be a transplacental carcinogen (CalEPA 2006), meaning that it can cross the placenta and cause cancer in the animal's offspring. For TCE, the US Department of Health and Human Services,

US EPA, and the IARC have all determined it to be a human carcinogen (ATSDR 2019; Guha et al. 2012; IARC 2014; NTP 2011; US EPA 2011). Epidemiological studies provide strong evidence that TCE can cause kidney cancer in humans and some evidence that it causes non-Hodgkin lymphoma and liver cancer. While most studies evaluate adult worker populations, children are expected to have similar health effects as adults (ATSDR 2019).

Although this study's risk estimates were not precise, the associations suggested with past NDMA and/or TCE drinking water exposures offer what we believe is a plausible explanation, supported by valid objective data, for the pattern of elevated cancer observed in areas of Wilmington, MA. The presence of these contaminants cannot definitively explain the pattern of childhood/adolescent cancer, but it should be recognized that despite the low statistical power of the study, several findings reported here do reach the traditional threshold of statistical significance, are plausibly supported by the literature, and could be real. However, as in any study, the statistical associations found could have been affected by bias or confounding or could be due to chance.

CRITERIA USED TO DRAW STUDY CONCLUSIONS

Statistical significance was used in this study as a tool to help identify potentially meaningful results. However, statistical significance was not the only criteria used to interpret results and draw conclusions; results that are not statistically significant may still be considered relevant. Careful consideration of the following contributed to all study conclusions:

- The magnitude of ORs

- The width of CIs

- P-values

- The presence or absence of dose-response trends

- The presence of consistency in the results

- The plausibility of an association based on the scientific literature

- The presence and potential impact of any confounding, measurement error, or bias.

CONCLUSIONS

Despite a number of limitations including a small sample size, an exposure assessment based on limited historical data of NDMA and TCE in the town's drinking water, and an inability to account for dietary NDMA exposure, the study was able to reach several important conclusions:

1. Comprehensive information on NDMA in groundwater and the historical Wilmington water distribution system enabled development of a computer model to predict the movement of NDMA to public water supply wells and in the water distribution system, enabling estimation of monthly NDMA concentrations at each study participant's residence between 1974 and 2000;

2. Detailed interviews of each participant and matched control provided information on major risk factors known or suspected from the published scientific literature for the types of cancer diagnosed among the Wilmington children and adolescents;

3. An association between maternal exposure to NDMA during the year before the child's birth and risk of that child developing cancer was strongly suggested by the results of this study. This association was statistically significant for the Leukemia/Lymphoma subgroup, marginally significant for the All Cancers group, and a dose-response effect was observed. We cannot rule out that this finding was confounded by exposure to TCE, but the effect is plausibly supported by the literature and could be a real one;

4. A positive association between maternal exposure to TCE during the year before the child's birth and risk of that child developing cancer was not statistically significant and a dose-response effect was not observed, meaning that we cannot rule out the possibility that the finding is due to chance, although it must also be recognized that the study was necessarily underpowered due to a small population and that the association is plausibly supported by the literature. It should also be noted that it is impossible to evaluate the effect of TCE alone using the data available;

5. Minimal evidence for an association between childhood/adolescent cancer and exposure to NDMA during childhood/adolescence was observed;

6. A statistically significant increased risk of cancer was observed among a small number of cases who were treated with oxygen immediately following birth, among a small number of cases born with low birth weight, and among all cases having any one of three reported adverse birth events (oxygen at birth, low birth weight, or incubation).