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Tetrachloroethylene-Contaminated Drinking Water and the Risk of Breast Cancer

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We conducted a population-based case-control study to evaluate the relationship between cases of breast cancer and exposure to tetrachloroethylene (PCE) from public drinking water ($n=258$ cases and 686 controls). Women were exposed to PCE when it leached from the vinyl lining of water distribution pipes. The relative delivered dose was estimated using an algorithm that accounted for residential history, water flow, and pipe characteristics. Only small increases in breast cancer risk were seen among ever-exposed women either when latency was ignored or when 5 to 15 years of latency was considered. No or small increases were seen among highly exposed women either when latency was ignored or when 5 years of latency was considered. However, the adjusted odds ratios (ORs) were more increased for highly exposed women when 7 and 9 years of latency, respectively, were considered (OR 1.5, 95% CI 0.5–4.7 and OR 2.3, 95% CI 0.6–8.8 for the 75th percentile, and OR 2.7, 95% CI 0.4–15.8 and OR 7.6, 95% CI 0.9–161.3 for the 90th percentile). The number of highly exposed women was too small for meaningful analysis when more years of latency were considered. Because firm conclusions from these data are limited, we recently undertook a new study with a large number of more recently diagnosed cases. — *Environ Health Perspect* 106(Suppl 4):947–953 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-4/947-953aschengrau/abstract.html>

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Introduction

Tetrachloroethylene (PCE) is one of the main chlorinated hydrocarbon solvents used in dry cleaning, textile processing, and metal degreasing (1). A 1989 National Institute for Occupational Safety and Health (NIOSH) survey estimated that more than 500,000 people in the United States are occupationally exposed to PCE (2). Because most of its use in occupational settings occurs in small, geographically dispersed, and poorly controlled facilities such as dry cleaning establishments, garages, and machine shops, PCE has become a common drinking water contaminant (1). Although industrial waste disposal is the main source of drinking water contamination, a different exposure scenario led to the

PCE contamination of the drinking water in the Cape Cod region of Massachusetts.

In January 1980, the Massachusetts Department of Environmental Protection (DEP) learned that PCE was leaching into drinking water from the inner vinyl lining of certain asbestos cement water distribution pipes (3). The vinyl resin liner had been introduced in the late 1960s in response to complaints about the taste and odor of water coming into contact with the asbestos cement pipes. The coating process consisted of brushing a vinyl resin slurry, including the solvent PCE, onto the interior surface of the pipe. The PCE was assumed to disappear in the drying process because of its volatility; however,

considerable quantities remained and slowly leached into the water.

Data gathered from the state's water departments indicated that approximately 660 miles of vinyl-lined/asbestos cement (VL/AC) pipes had been installed (3). A large proportion had been introduced in the five towns of the upper Cape Cod area (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich). Typical levels in affected pipes in the town of Falmouth, which had 50 miles of VL/AC pipes installed, varied from 1600 to 7750 $\mu\text{g}/\text{l}$ at low-use locations to 1.5 to 80 $\mu\text{g}/\text{l}$ at medium- and high-use locations (4). To rectify the problem the Massachusetts DEP began a regular timetable of flushing and continuous bleeding. The goal was to lower the levels below 40 $\mu\text{g}/\text{l}$ based on the U.S. Environmental Protection Agency's suggested no adverse response level at the time. However, by the time these risk management procedures were implemented, thousands of residents had already been drinking PCE contaminated water, some for as long as a decade.

Several years after the PCE contamination was discovered the Massachusetts Department of Public Health reported elevations in cancer mortality in the upper Cape Cod area during the years from 1969 to 1983 (5). When the Massachusetts Cancer Registry (Boston, MA) began monitoring cancer incidence in 1982, statistically significant excesses were also seen in the incidence rate of many cancers, including those of the breast, colon/rectum, lung, and blood-forming organs, among residents of the upper Cape region as compared to state average (6).

In response to public concern regarding the elevated cancer rates and pollution in the upper Cape Cod area, we undertook a population-based case-control study to evaluate the relationship between nine types of cancer (lung, breast, colorectal, bladder, kidney, pancreas, brain, liver, and leukemia) and air and water pollution including exposure to PCE-contaminated drinking water (7–9). Exposure to PCE-contaminated water was initially examined in relation to three of the cancer sites—bladder, kidney, and leukemia—because previous studies of occupationally exposed individuals found associations with these cancers (2,10–15).

Our prior study found an elevated relative risk of leukemia among ever-exposed subjects (odds ratio [OR] 1.96, 95% confidence interval [CI] 0.71–5.37 considering

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Abbreviations used: CI, confidence interval; DEP, Department of Environmental Protection; HCFA, Health Care Financing Administration; NIOSH, National Institute for Occupational Safety and Health; OR, odds ratio; PCE, tetrachloroethylene; RDD, relative delivered dose; SMR, standardized mortality ratio; VL/AC, vinyl-lined/asbestos cement.

a 5-year latency and OR 2.13, 95% CI 0.88–5.19 without latency) that rose further among subjects whose exposure level was above the 90th percentile (OR 5.84, 95% CI 1.37–24.91 with latency and OR 8.33, 95% CI 1.53–45.29 without latency) (9). An elevated relative risk of bladder cancer was also observed among subjects whose exposure level was above the 90th percentile when latency was ignored (OR 4.03, 95% CI 0.65–25.10). These elevated risks were present after controlling for numerous confounding variables including age, gender, vital status at interview, and occupational exposure to PCE, benzene, and other solvents.

Subsequently, we undertook another study to examine exposure to PCE-contaminated water in relation to the remaining six cancers from the original case-control study. This paper presents the methods and results for the breast cancer analysis.

Methods

Selection and Enrollment of Study Population

Cases were incident cancers of the breast ($n = 334$) diagnosed from 1983 through 1986 among permanent residents of five towns in the upper Cape Cod area and reported to the Massachusetts Cancer Registry. Controls were selected from demographically similar permanent residents of the upper Cape Cod towns during the years from 1983 to 1986. Three sources were needed to identify controls efficiently, as many cases were elderly or deceased when the study began. Living controls under 65 were chosen using random-digit dialing, and those aged 65 and over were chosen randomly from lists of Medicare beneficiaries furnished by the Health Care Financing Administration (HCFA). Deceased controls of similar age as deceased cases were chosen randomly from a file furnished by the Massachusetts Department of Vital Statistics and Research.

Random-digit dialing was used to select a random sample of living telephone subscribers under 65 years of age who lived in the five upper Cape Cod towns during years the cases were diagnosed. According to the 1980 U.S. Census (16), more than 95% of housing units in Massachusetts had telephone service. A total of 2236 residential households were identified using this technique (Table 1). Approximately 63% did not have any residents who met the inclusion criteria. An additional 20% never answered the phone after many calls, and

Table 1. Selection and enrollment of breast cancer cases and controls.

	Cases	HCFA	Controls deceased	Random-digit dial
Selected	334	611	918	2236
Excluded				
Never located or contacted	33	21	97	456
Ineligible	6	53	27	1531
Physician or subject refusal	30	73	71	65
Interviewed	265	464	723	184

about 6% would not respond to the screening questions that determined eligibility. Ultimately, 249 households were found with an eligible resident.

Because random-digit dialing is not an efficient way to identify elderly individuals, living controls 65 years of age and older were selected from a file of Medicare recipients provided by the HCFA. Hatten estimated that Medicare recipients comprise 95% of individuals aged 65 years and older in the United States (17). Six hundred eleven HCFA controls were randomly chosen from residents of the five upper Cape Cod towns using an age- and gender-stratified sampling scheme. Before interviews, the vital status and residence of HCFA controls during the case ascertainment period were determined and all deceased individuals and non-upper Cape Cod residents were eliminated.

Controls who died between 1 January 1983 and 31 December 1989 were randomly chosen from a file of all deaths that occurred among residents of the five upper Cape Cod towns. All individuals, irrespective of the cause of death, were eligible for selection. Nine hundred eighteen deceased controls were chosen using a scheme that stratified on age, gender, and year of death. The deceased control's residence during the case ascertainment period was determined before the interview and all nonresidents were eliminated.

Up-to-date addresses and telephone numbers of subjects, and, if necessary, their relatives, were identified from Cancer Registry and HCFA records, physicians, tumor registrars, Department of Vital Statistics' death, birth, and marriage records, state voter registration lists and drivers' license records, telephone books, and directory assistance. Following Cancer Registry policy, permission was obtained from treating physicians before interviewing living cases.

After obtaining informed consent, trained staff carried out structured interviews to obtain a 40-year residential history, information on demographic characteristics, confounding variables such as age, family

history of breast cancer, age at first live birth or stillbirth, prior history of breast cancer and benign breast disease, occupational history, including exposure to PCE, benzene, and other solvents, bottled water consumption, and usual bathing habits. To determine typical bathing habits, subjects were asked if they took mostly showers, mostly baths, or showers and baths about equally, when at home.

Job titles and industries were coded using the *Standard Industrial Classification Manual* (18) and the *Standard Occupational Classification Manual* (19). Occupational exposure to PCE and related solvents was estimated using both direct questions from the interview and industry and job title information.

Overall, 79% of the cases, 76% of HCFA controls, 79% of deceased controls, and 74% of contacted and eligible random-digit dial controls were interviewed. The demographic characteristics of interviewed and noninterviewed subjects were similar. The site-specific control group for the breast cancer analysis was selected, first by stratifying the breast cancer cases on the basis of age (in decades), gender, vital status, and if deceased, year of death, and then by choosing all controls who fell into a stratum with at least one case. This strategy yielded 763 breast cancer controls.

Next, index years were randomly assigned to the controls that were comparable to the cases' diagnosis dates. Assignment was weighted to achieve identical distributions of diagnosis and index years. Only exposures of control subjects that occurred before the index year were counted. Controls who moved to the upper Cape Cod area after the index year ($n = 46$) and cases ($n = 7$) and controls ($n = 31$) with incomplete residential histories were excluded, leaving 258 breast cancer cases and 686 controls for the final analysis.

Tetrachloroethylene Exposure Estimation

Relative exposure to PCE-contaminated drinking water was estimated with an

algorithm developed by Webler and Brown (20) that used information about the water pipe supplying each subject's upper Cape Cod residence. Relative exposure, termed the relative delivered dose (RDD), was defined as the estimated mass of PCE (in milligrams) that entered a house as a drinking water solute during a specified time period. The word relative is used to stress that the number is an ordinal estimate rather than an accurate determination.

The algorithm for estimating the RDD is based on a model for PCE leaching from vinyl-lined pipe proposed and tested by Demond (4). Briefly, the initial amount of PCE in a pipe is directly proportional to its inside surface area. The rate at which the initial stock leaches depends on the physical characteristics of the pipe and the water flow, including its temperature, density, viscosity, and flow rate. The Webler-Brown algorithm (20) estimates a pipe's initial stock of PCE from its length and diameter, and the leaching rate from the water flow and age of the pipe.

The flow rate is affected by the geometry of the water distribution system and the load on the system. The Webler-Brown algorithm (20) streamlined the effects of geometry by considering four generic cases: dead ends, circles, circles with taps, and in-line. Any specific case was considered to be either one or a combination of these geometries. The pipe load depends on the number of connected houses, the date of connection, and the water consumption of each house. Tax assessment and water distribution system maps were used to ascertain the spacing of house connections. Water flow was assumed to be unidirectional and all houses were assumed to draw the same amount of water during a subject's residency.

To implement Webler and Brown's model (20), the locations of the VL/AC pipes in all public water supply systems in the area were determined. Five of the 11 water suppliers reported that there were no VL/AC pipes in their districts. The remaining 6 suppliers provided water distribution maps showing the location of the VL/AC pipes and their installation dates.

Next, all subject residences on VL/AC streets were identified and located on the distribution network. For every residence on a VL/AC street, a schematic was made depicting water flow to the residence. Each schematic also displayed the location and number of loads, pipe length(s), and installation date(s). Once the schematic was developed, the variables were entered into a database management system that was

programmed to check for inconsistencies and then calculate the RDD. All entered data were double checked for accuracy.

Developing the schematic often involved judgment of water distribution characteristics not provided by the water suppliers. Water flow direction was determined by inspecting various features of the distribution network including water source locations and pipe sizes, whereas determining the load distribution required judging the point where residences connected to water mains. A protocol was designed so that all decisions were made in a consistent manner. In addition, all exposure assessments were conducted without knowing who was a case or who was a control.

Data Analysis

The analysis first compared ever-exposed versus never-exposed women, then never-exposed women were compared to women with low and high cumulative RDDs. Low RDD was defined as an exposure level up to and including the median (50th percentile) cumulative RDD among the exposed women. The exposure distribution above the median was further categorized into three overlapping categories—above the 50th, 75th, and 90th percentile—to signify successively higher levels of exposure. The reference group always consisted of never-exposed subjects.

Because it was possible that PCE might act either as a tumor initiator, a tumor promoter, or both, analyses were conducted considering and ignoring a latent period. Several latent periods were considered (5, 7, 9, 11, 13, and 15 years) because it was unknown when measurable effects might occur. More than 15 years of latency was not considered because the number of exposed subjects was too small for meaningful analysis.

Women were considered exposed if they had at least one exposed residence during the relevant period. If a woman had more than one exposed residence, RDDs were cumulated over all of them. The cumulative exposure during the relevant period was calculated for each latency assumption. For example, cumulative exposure that occurred more than 5 years before the diagnosis or index year was counted when the 5-year latency interval was applied.

The exposure OR was used to estimate the strength of the relationship (relative risk) between PCE exposure and the occurrence of breast cancer. The potential modifying effects of menopausal status, drinking

bottled water, and bathing habits were examined in stratified analyses. Ninety-five percent CIs were calculated to assess the statistical stability of the crude associations.

Multiple logistic regression was used to control simultaneously for potential confounding variables (21). The antilog of the beta coefficient of the exposure variable served as an estimate of the OR. A group of core confounders was included in all multivariate models, consisting of age at diagnosis or index year, vital status at the interview, family history of breast cancer, age at first live birth or stillbirth, personal history of prior breast cancer and benign breast disease, and occupational exposure to PCE, benzene, and other solvents. Other potential confounders were added to the multivariate models along with the core confounders. None changed the adjusted ORs by more than 10% so they were not included in the final model. Ninety-five percent CIs for the adjusted ORs were calculated using the maximum likelihood estimates of the standard errors (22).

Results

Overall, the women in the study were predominantly Caucasian, elderly, and educated beyond high school (Table 2). The distribution of several variables associated with breast cancer risk was as expected, with more cases than controls reporting a family history of breast cancer, nulliparity, and late age at first birth. However, fewer cases than controls reported a history of breast cancer and benign breast disease. A small and similar proportion of cases and controls was classified as having occupational solvent exposure and reported drinking bottled water on a regular basis before the diagnosis or index year. Finally, more cases than controls reported taking showers whereas fewer cases than controls reported taking baths.

A total of 14.0% of cases ($n=36$) and 11.8% of controls ($n=81$) were classified as ever exposed to PCE-contaminated drinking water when latency was ignored and from 0% to 9.7% of cases ($n=0-25$) and 0.6% to 8.2% of controls ($n=4-56$) were classified as ever exposed when 5 to 15 years of latency were considered (Table 3). When latency was ignored, RDD estimates obtained from the Webler-Brown model ranged from 0.004 to 335.5, and estimates at the median, 75th, and 90th percentiles were 9.1, 28.9, and 53.4, respectively (Table 4). The maximum RDD became lower as more years of latency were taken into account (e.g., the

Table 2. Distribution of selected characteristics of breast cancer cases and controls, %.

Characteristic	Cases, n=258	Controls, n=686
Caucasian	98.4	96.8
Age at diagnosis or index year, years		
1-49	12.0	7.1
50-59	14.0	10.2
60-69	31.4	33.1
70-79	26.4	29.4
80+	16.3	20.1
Educational level at least 12 years	83.1	82.7
Alive at interview	67.4	55.1
Age at first live birth or stillbirth		
<30 years	55.4	61.9
30+ years	14.0	13.3
Nulliparous	30.6	24.8
Prior breast cancer or benign breast disease ^a	14.5	23.2
Family history of breast cancer	19.2	8.8
Postmenopausal	88.0	92.0
Ever had occupational exposure to solvents	13.2	10.5
Regularly drank bottled water before diagnosis or index year	10.9	8.9
Usual bathing habits		
Mostly showers	37.2	30.5
Mostly baths	39.5	46.6
About equal	18.6	19.8

^aBefore current diagnosis for cases.

Table 3. Tetrachloroethylene exposure history of breast cancer cases and controls, crude odds ratios, and 95% confidence intervals.

Latency period, years	PCE-exposed cases, n=258	PCE-exposed controls, n=686	Odds ratio ^a	95% CI
0	36	81	1.2	0.8-1.8
5	25	56	1.2	0.7-2.0
7	17	39	1.2	0.6-2.1
9	14	25	1.5	0.8-2.9
11	7	18	1.1	0.4-2.5
13	4	7	1.6	0.4-5.2
15	0	4	0.0	-

^aThe exposure OR was calculated relative to never-exposed cases (n=222) and controls (n=605).

Table 4. Distribution of cumulative relative delivered doses among tetrachloroethylene-exposed subjects according to latency period.

Latency period, years	Exposed subjects, no.	Minimum	Maximum	Median	75th Percentile	90th Percentile
0	117	0.004	335.3	9.1	28.9	53.4
5	81	0.02	314.4	11.8	29.6	51.8
7	56	0.3	280.8	11.4	31.1	50.5
9	39	0.6	199.0	8.6	30.6	55.2
11	25	0.5	154.3	14.4	26.4	46.7
13	11	2.1	139.0	12.4	24.2	76.9
15	4	1.6	124.1	11.1	70.8	124.1

maximum RDD was 124.1 when 15 years of latency was considered). However, the cutoffs for the median, 75th, and 90th percentiles were generally stable across the various latency assumptions.

Only small increases in the crude OR for breast cancer were observed among ever-exposed subjects both when latency was ignored and when it was taken into account (ORs 0.0-1.6; Table 3). When the

level of exposure was dichotomized at the median, no or only small increases in the crude OR were seen among women whose exposure levels were either below or above the median (ORs 0.9-1.8; Table 5). The results were mixed when the most highly exposed women were examined. No or only small increases in risk were seen among women whose exposures were above the 75th and 90th percentiles either when latency was ignored or when 5 years of latency were taken into account. However, the ORs were increased when 7 and 9 years of latency, respectively, were taken into account (OR 2.0, 95% CI 0.7-5.9 and OR 2.7, 95% CI 0.8-9.9 for the 75th percentile, and OR 2.7, 95% CI 0.5-14.8 and OR 8.2, 95% CI 1.0-165.7 for the 90th percentile). No increases were seen among the most highly exposed women when 11 and 13 years of latency were taken into account, but the number of exposed subjects was extremely small.

Most relative risk estimates changed only slightly when confounding variables were controlled using multiple logistic regression models (Table 6). When 7 and 9 years of latency were taken into account, the adjusted relative risks were 1.5 (95% CI 0.5-4.7) and 2.3 (95% CI 0.6-8.8), respectively, among women whose exposure level was above the 75th percentile, and 2.7 (95% CI 0.4-15.8) and 7.6 (95% CI 0.9-161.3), respectively, among women whose exposure level was above the 90th percentile.

Too few women reported that they drank bottled water on a regular basis before their diagnosis or index year to describe the relationship between PCE exposure and breast cancer occurrence among these women. Nonetheless, the relative risks were similar when the analysis was restricted to subjects who never drank bottled water regularly. In addition, no important differences in risk were observed in relation to a woman's usual bathing habits but the number of subjects in each bathing category was quite small.

There were also too few premenopausal women to examine these subjects separately. With the following exceptions, the ORs were similar when the analysis was restricted to postmenopausal subjects (Table 7). Compared to never-exposed women, increases in the adjusted ORs were seen among postmenopausal women regardless of the exposure level when 13 years of latency was taken into account, and among postmenopausal women whose exposure level was above the 90th percentile when

Table 5. Crude odds ratios for breast cancer according to various tetrachloroethylene exposure levels.

Latency period, years	PCE exposure level			
	≤ Median, case/control, no. OR (95% CI)	> Median, case/control, no. OR (95% CI)	>75th Percentile, case/control, no. OR (95% CI)	>90th Percentile, case/control, no. OR (95% CI)
0	17/41 1.1 (0.6–2.0)	19/40 1.3 (0.7–2.3)	8/21 1.0 (0.4–2.3)	4/8 1.4 (0.4–4.4)
5	13/27 1.3 (0.6–2.5)	12/29 1.1 (0.5–2.2)	7/13 1.5 (0.5–3.6)	3/5 1.6 (0.3–6.7)
7	8/20 1.1 (0.4–3.2)	9/19 1.3 (0.5–2.8)	6/8 2.0 (0.7–5.9)	3/3 2.7 (0.5–14.8)
9	6/13 1.3 (0.4–3.2)	8/12 1.8 (0.7–4.5)	5/5 2.7 (0.8–9.9)	3/1 8.2 (1.0–165.7)
11	3/9 0.9 (0.2–3.1)	4 / 9 1.2 (0.3–3.8)	1/5 0.5 (0.0–3.4)	0/2 0.0 (–)
13	2/3 1.8 (0.2–11.0)	2/4 1.4 (0.2–7.0)	0/3 0.0 (–)	0/1 0.0 (–)

Table 6. Adjusted odds ratios for breast cancer according to various tetrachloroethylene exposure levels.

Latency period, years	PCE exposure level, OR (95% CI)				
	>Zero	≤ Median	>Median	>75th Percentile	>90th Percentile
0	1.1 (0.7–1.7)	1.0 (0.5–1.8)	1.1 (0.6–2.0)	0.8 (0.3–1.8)	1.1 (0.3–3.8)
5	1.1 (0.6–1.8)	1.2 (0.6–2.4)	0.9 (0.4–1.9)	1.2 (0.4–3.0)	1.5 (0.3–6.4)
7	1.0 (0.5–1.9)	1.0 (0.4–2.4)	1.0 (0.4–2.3)	1.5 (0.5–4.7)	2.7 (0.4–15.8)
9	1.4 (0.7–2.7)	1.1 (0.4–3.1)	1.6 (0.6–4.1)	2.3 (0.6–8.8)	7.6 (0.9–161.3)
11	0.9 (0.3–2.1)	0.7 (0.1–2.5)	1.0 (0.3–3.3)	0.6 (0.0–3.7)	0.0 (–)
13	1.5 (0.4–5.2)	1.5 (0.2–10.2)	1.4 (0.2–7.8)	0.0 (–)	0.0 (–)

Table 7. Adjusted odds ratios for breast cancer among postmenopausal women according to various tetrachloroethylene exposure levels.

Latency period, years	PCE exposure level, OR (95% CI)				
	>Zero	≤ Median	>Median	>75th Percentile	>90th Percentile
0	1.1 (0.7–1.7)	1.1 (0.6–2.0)	1.1 (0.6–2.1)	0.6 (0.2–1.6)	1.1 (0.2–4.2)
5	1.0 (0.6–1.8)	1.2 (0.6–2.5)	0.9 (0.4–1.9)	1.0 (0.3–3.0)	2.0 (0.4–9.8)
7	1.2 (0.6–2.2)	1.2 (0.5–2.8)	1.1 (0.4–2.8)	1.5 (0.4–5.7)	4.8 (0.7–40.1)
9	1.5 (0.7–3.2)	1.1 (0.3–3.2)	2.0 (0.7–5.7)	3.4 (0.7–19.1)	7.8 (0.9–167.0)
11	0.9 (0.3–2.4)	0.6 (0.1–2.5)	1.2 (0.2–5.0)	1.2 (0.1–10.6)	0.0 (–)
13	2.3 (0.5–9.4)	2.4 (0.3–23.3)	2.2 (0.3–14.3)	0.0 (–)	0.0 (–)

5, 7, and 9 years of latency were taken into account.

Discussion

The results of this study suggest that women with high relative delivered doses of PCE-contaminated drinking water have an increased risk of breast cancer, particularly when the cancer occurs during the postmenopausal years. These results should be interpreted cautiously because the increased risk was observed only when 7 and 9 years of latency were taken into account and the proportion of exposed subjects was small. In fact, insufficient numbers hampered our ability to extend the latency analysis beyond 9 years.

Because the exposures occurred many years ago, it is not possible to determine with certainty the exact PCE levels to which the women were exposed. Our exposure estimates were based on the Weblert-Brown model. Any false assumptions about the model or errors determining the model variables would have led to errors in estimating the RDDs. Even if the PCE concentration of the drinking water that entered the house was correctly estimated, women were likely to ingest and come into contact with differing amounts of water at home depending on their personal habits. Furthermore, no information was available on possible workplace exposures. Because exposure estimation was conducted blindly,

it is likely that any estimation errors occurred both among cases and controls and so biased the ORs toward the null.

It is improbable that the observed results are due to confounding, observation, or selection bias. Age at diagnosis or index year, vital status at interview, occupational exposure to PCE, benzene, and other solvents, and many traditional breast cancer risk factors were controlled in a multivariate analysis. Residual confounding by other sources of pollution, including drinking-water contaminants, is an unlikely explanation of the results. These risk factors would have to be strong risk factors for breast cancer, closely correlated with PCE exposure, and sufficiently common to have produced the increased ORs seen in this study. In fact, no vinyl chloride and very low levels of benzene were detected in public drinking-water supplies during the study period, and trihalomethanes were generally low, as only one supplier chlorinated the water. In addition, no association was observed between breast cancer and exposure to either the chlorinated surface water supply or the groundwater supplies with evidence of contamination.

It is also unlikely that the findings were influenced by systematic differences in the interviewing technique. Although the interviewers knew the disease status of the women, they were well trained and the interview was pretested and standardized. In addition, systematic differences in recall between cases and controls were not likely, as deceased controls who had proxy interviews in the same manner as deceased cases were selected and PCE exposure estimation was conducted independently of the interview.

Selection bias is also implausible because the breast cancer cases were obtained from reports of incident cases to the Massachusetts Cancer Registry. Comparison with rates in Connecticut and other registries indicate nearly complete reporting (6). In addition, follow-up and interview rates were similar for cases and controls, and the demographic characteristics of participants and nonparticipants were similar.

Based on the evidence in experimental animals and humans, PCE is considered probably carcinogenic to humans (Group 2A) by the International Agency for Cancer Research (23) and on a continuum between probably and possibly carcinogenic by the U.S. Environmental Protection Agency (currently under review). The animal evidence includes hepatocellular

carcinomas associated with both oral and respiratory exposures in mice and mononuclear cell leukemia and renal cancer associated with respiratory exposure in rats. To the best of our knowledge, none of the animal experiments found an increased incidence of mammary tumors (23). In addition, PCE was found to be nonestrogenic in at least one bioassay for determining the estrogenic activity of environmental pollutants (24).

Much of the epidemiologic evidence comes from mortality studies of dry-cleaning workers, where PCE has been the main solvent since the 1960s. The epidemiologic studies suggest associations of dry cleaning and laundry work with leukemia, uterine, cervical, lung, colon, pancreatic, liver, esophageal, and bladder cancer (2,10–15). The breast cancer results are summarized below.

A proportional mortality study of 671 female dry cleaning and laundry workers in Wisconsin found a decreased proportion of breast cancer deaths (proportional mortality rate 72; 27 observed vs 37.4 expected) (10). Another proportional mortality study of laundry and dry cleaning workers in Oklahoma also found a deficit of breast cancers (standardized mortality OR 0.1, 1 observed death vs 10.5 expected); however, the number of women in the cohort of 440 was not given (11).

A U.S. National Cancer Institute mortality study of dry cleaners' union members ($n=4046$ women) also found no increased risk of mortality due to breast cancer (standardized mortality ratio [SMR] 100, 36 observed vs 36.3 expected) (13). However, a NIOSH mortality study of 1109 women employed in dry cleaning shops where PCE was the primary solvent found a slight increase (8%) in the breast cancer death rate (95% CI 0.65–1.69) that stemmed mainly from exposures occurring 20 years or more before (SMRs 1.21 and 1.45 for durations of employment < 5 and ≥ 5 years with ≥ 20 years of latency) (2). Although no increased risk of breast cancer mortality was seen among the subcohort exposed only to PCE (SMR 1.00, 95% CI 0.36–2.17), the number of women in this group was small ($n=414$) and no latency analyses were conducted in this subgroup.

Although these breast cancer results are mainly null, the studies suffer from the usual limitations of mortality studies, including exposure misclassification, lack of control of key confounders (with one exception), small numbers of women, inaccurate death certificate data, and the inability to examine diseases that are not often fatal.

Because firm conclusions on the relationship between PCE-contaminated drinking water and breast cancer in our

study were limited by the small proportion of exposed subjects, particularly when longer latent periods were considered, we undertook a larger study of this relationship in 1995 with funding from the Superfund Basic Research Program. Our new population-based case-control study includes approximately 850 incident breast cancers diagnosed from 1987 to 1993 among permanent residents of eight Cape Cod towns (Barnstable, Bourne, Falmouth, Mashpee, Sandwich, Brewster, Chatham, and Provincetown) and approximately 850 controls from the resident population. The subject selection and exposure assessment methods are similar to those in this paper. However, more detailed information on water consumption and bathing patterns is being obtained at the interviews. The 5-year study is scheduled for completion in the year 2000.

Like the "vast natural experiment" of Snow's cholera investigation in 1854 London (25), the unusual exposure scenario in the Cape Cod region gives us a unique opportunity to learn more about the health effects of PCE exposure in a community setting. The new study should also make a meaningful contribution to the body of scientific evidence on the relationship between breast cancer and exposures in the environment where people actually live.

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