Perchloroethylene-Contaminated Drinking Water and the Risk of Breast Cancer: Additional Results from Cape Cod, Massachusetts, USA

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In 1998 we published the results of a study suggesting an association between breast cancer and perchloroethylene (PCE; also called tetrachloroethylene) exposure from public drinking water. The present case–control study was undertaken to evaluate this association further. The cases were composed of female residents of eight towns in the Cape Cod region of Massachusetts who had been diagnosed with breast cancer from 1987 through 1993 (n = 672). Controls were composed of demographically similar women from the same towns (n = 616). Women were exposed to PCE when it leached from the vinyl lining of water distribution pipes from the late 1960s through the early 1980s. A relative delivered dose of PCE that entered a home was estimated using an algorithm that took into account residential history, water flow, and pipe characteristics. Small to moderate elevations in risk were seen among women whose exposure levels were above the 75th and 90th percentiles when 0–15 years of latency were considered (adjusted odds ratios, 1.5–1.9 for > 75th percentile, 1.3–2.8 for > 90th percentile). When data from the present and prior studies were combined, small to moderate increases in risk were also seen among women whose exposure levels were above the 75th and 90th percentiles when 0–15 years of latency were considered (adjusted odds ratios, 1.6–1.9 for > 75th percentile, 1.3–1.9 for > 90th percentile). The results of the present study confirm those of the previous one and suggest that women with the highest PCE exposure levels have a small to moderate increased risk of breast cancer. *Key words:* breast cancer, drinking water, perchloroethylene, pollution, tetrachloroethylene. *Environ Health Perspect* 111:167–173 (2003). [Online 25 October 2002]

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Perchloroethylene (PCE; also called tetrachloroethylene) is a chlorinated solvent commonly used in industrial operations such as dry cleaning, textile processing, and metal degreasing [Agency for Toxic and Substances and Disease Registry (ATSDR) 1995]. Because PCE is mainly used in small, geographically scattered, and poorly controlled workplace settings, it has become a common contaminant of drinking water and Superfund sites.

Although industrial disposal is the typical source of drinking water contamination, PCE leached into the drinking water supplies of Cape Cod, Massachusetts, from an inner vinyl liner that was present in certain asbestos cement pipes (Larsen et al. 1983). The vinyl liner was introduced in the late 1960s in response to taste and odor complaints. A slurry of a vinyl plastic and PCE was used to coat the inside of the pipes just before shipping. The manufacturers assumed that the volatile PCE would disappear during the drying process; however, substantial quantities remained and slowly leached into the drinking water supplies.

More than a decade lapsed before the Massachusetts Department of Environmental Protection (DEP) learned that the vinyl liner was a source of PCE contamination. A survey in 1979 revealed that 660 miles of the vinyl-lined asbestos cement (VL/AC) pipe had been installed in Massachusetts, predominantly in the Cape Cod region (Massachusetts Department of Environmental Quality Engineering 1982). Typical levels in affected towns ranged from 1,600 to 7,750 µg/L in low-flow locations, and from 1.5 to 80 µg/L in medium- and high-flow locations (Demond 1982). DEP began a regular program of flushing and bleeding to correct the problem in 1980.

In response to public concern about elevated cancer rates and environmental pollution in the Cape Cod area, we conducted a population-based case–control study to evaluate the relationship between nine types of cancer and air and water pollution, including PCE-contaminated drinking water (Aschengrau et al. 1998; Paulu et al. 1999). Although our study suggested that women with high relative delivered doses (RDDs) of PCE-contaminated drinking water have an increased risk of breast cancer, firm conclusions were limited by the small proportion of exposed subjects, particularly when long latent periods were considered. We undertook the present study with a larger number of more recently diagnosed cases in order to evaluate further the hypothesis that PCE exposure increases the risk of breast cancer. The biologic rationale for our study stems from a hypothesis recently described by Labreche and Goldberg (1997) that organic solvents such as PCE may act either directly as genotoxic agents or indirectly through their metabolites to increase the risk of breast cancer.

Materials and Methods

Selection and enrollment of study population. The case group was composed of women diagnosed with breast cancer from 1987 through 1993 who were permanent residents of eight Cape Cod towns (Barnstable, Bourne, Brewster, Chatham, Falmouth, Mashpee, Provincetown, and Sandwich) and whose diagnosis was reported to the Massachusetts Cancer Registry. Comparison of the Massachusetts Cancer Registry with other state cancer registries indicates nearly complete ascertainment for breast cancer (Massachusetts Department of Public Health 1995). For the vast majority of cases (94.6%) this was the first occurrence of breast cancer, but for a small percentage (5.4%) this was the second occurrence of a primary tumor.

The control group was composed of similarly aged women who were also permanent residents of the eight Cape Cod towns during 1987 through 1993. Because most cases were elderly and many were deceased at the start of data collection, three sources were used to identify controls in an efficient manner: *a*) living controls ≤ 64 years of age were selected by random-digit dialing; *b*) living controls ≥ 65 years of age were randomly selected from a roster of Medicare beneficiaries provided by the Health Care Financing Administration (HCFA); and *c*) deceased controls were randomly selected from a roster of deceased residents of the eight Cape Cod towns provided by the Massachusetts Bureau of Health Statistics, Research, and Evaluation. The number of controls selected from each source was weighted to reflect the age and vital status distribution among cases.

Random-digit dialing identified a random sample of female telephone subscribers ≤ 64 years of age who lived in the study

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towns during 1987–1993. According to the 1990 Census, 97% of housing units in Massachusetts have telephone service (Bureau of the Census 1990). A total of 3,402 residences were identified using this method (Table 1). Approximately 68% did not have any residents who met the eligibility criteria, and another 9% would not respond to the eligibility-determining questions. About 15% never answered the telephone after many calls. Ultimately, 248 households were found with an eligible respondent.

Living controls ≥ 65 years of age were identified using a roster of female Medicare beneficiaries provided by HCFA. Hatten (1980) has estimated that Medicare beneficiaries constitute 95% of the U.S. population ≥ 65 years of age. HCFA controls (n = 468) were randomly selected from residents of the eight Cape Cod towns using a sampling scheme that frequency matched on age.

Controls who died from January 1987 through December 1996 were randomly selected from deaths occurring to female residents of the study towns. Individuals with any cause of death were eligible. Deceased controls (n = 234) were selected using a sampling scheme that was frequency matched on age and year of death.

All subject selection and enrollment procedures were approved by the Institutional Review Boards of Boston University Medical Center, the Massachusetts Cancer Registry, and the HCFA.

Up-to-date addresses and telephone numbers of subjects and, if needed, next-of-kin were determined using cancer registry and HCFA records, physicians and tumor registrars, birth and death records, voter registration lists, driver's license records, telephone books, directory assistance, Internet resources, and obituary notices in local newspapers. Following Massachusetts Cancer Registry guidelines, permission was obtained from physicians of living cancer cases before conducting the interview.

After obtaining verbal consent, trained interviewers conducted structured interviews to obtain information on demographic characteristics, confounding variables including family history of breast cancer, occupational exposure to PCE, and a 40-year residential history. Information was also obtained on tap and bottled water consumption, bathing habits, drinking water source, and use of drinking-water treatment devices.

Index years were randomly assigned to the controls according to the distribution of diagnosis years among the cases. Subjects who reported that they moved to the study area after their diagnosis or index year were excluded. Exposures occurring after the diagnosis or index year were not counted.

Overall, 80.7% of selected and eligible cases, 76.4% of the HCFA controls, 79.0% of the deceased controls, and 82.6% of eligible and contacted random-digit dial controls were included in the analysis (Table 1). The reasons for exclusion were failure to be located, to meet the eligibility criteria, and to obtain permission for an interview from a treating physician (cases only); subject refusal; reaching the target number of interviews (random digit dial controls only); and unknown PCE exposure status. This produced 672 cases and 616 controls for the analysis.

The racial and vital status and geographic distributions of included and excluded eligible cases and non–random digit dial controls were quite similar. However, excluded subjects tended to be older than included subjects (e.g., 55% and 58% of excluded cases and non–random digit dial controls, respectively, were ≥ 70 years of age).

PCE exposure estimation. Relative exposure to PCE-contaminated water was estimated using an algorithm developed by Webler and Brown (1993) that took into account specific information about the water pipe that supplied each subject's Cape Cod home. An ordinal estimate of exposure to PCE-contaminated water, the relative delivered dose (RDD), was defined as the estimated mass of PCE that entered the home through the drinking water during a specified period. The algorithm for estimating the RDD is based on a model for PCE leaching from vinyl-lined pipe that was developed by Demond (1982). The model assumes that the initial amount of PCE in a pipe is proportional to its inner surface area. The rate at which the initial stock leaches depends on the physical characteristics of the pipe and the water flow. Thus, the Webler-Brown algorithm estimates the pipe's initial stock from its diameter and length, and the leaching rate from the age of the pipe and water flow, including the flow rate (Webler and Brown 1993).

The water flow rate is influenced by the geometry and load on the water distribution system. The Webler-Brown algorithm simplified the effect of geometry by considering four generic cases: dead ends, circles, circles with taps, and in-line (Webler and Brown 1993). A specific subject was considered as 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. Computerized parcel and street maps obtained from local authorities were used to determine the location and spacing of the house connections. The time of a household's connection to public drinking water was determined from subject interviews. Subjects who stated that their household was served by a private well for their entire Cape Cod residency (n = 14) were considered unexposed. Water flow was

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

	Cases	HCFA controls	Deceased controls	Random digit dial controls
Selected	858	468	234	3,402
Excluded				
Never located or contacted	54	16	20	515
Ineligible[a]	25	74	34	2,639
Physician not located or refused	41	—	—	—
Subject refusal	65	77	19	33
Target reached[b]	—	—	—	58
PCE exposure status unknown	1	—	3	—
Included in analysis	672	301	158	157

[a]Includes cases and non–random digit dial controls who did not meet residence criteria (n = 98), cases without breast cancer (n = 2), HCFA controls who died (n = 33), and random digit dial controls who did not meet the age, sex, and residence criteria (n = 2,319) or who refused to answer the eligibility questions (n = 320). [b]These random digit dial controls were identified as eligible but not contacted for interview because the target number of random digit dial controls had already been interviewed.

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

Characteristic	Cases (n = 672)	Controls (n = 616)
White	98.4	95.8
Age at diagnosis or index year (years)		
1–49	16.5	16.7
50–59	12.2	13.6
60–69	31.5	29.9
70–79	28.4	26.0
≥ 80	11.3	13.8
Educational level ≥ 12 years	90.2	87.4
Alive at interview	71.9	74.4
Age at first live birth or stillbirth		
< 30 years	61.0	66.8
≥ 30 years	14.5	12.8
Nulliparous	24.5	20.4
Prior breast cancer[a]	5.4	4.8
Prior benign breast disease[b]	24.9	20.6
Family history of breast cancer[c]	25.6	15.5
Postmenopausal at diagnosis or index year	88.7	84.6
Definite or possible occupational exposure to PCE[b,d]	15.5	14.8
Residence near dry cleaner[b]	0.6	0.2
Bathing habits[b,e]		
Only baths	12.7	15.9
Only showers	40.6	35.6
Both baths and showers	46.7	48.5
Regularly drank bottled water[b,e]	28.2	27.7
Used a water treatment device[b,e]	12.9	13.7

[a]These women had a prior breast cancer diagnosis before current diagnosis year for cases and index year for controls. [b]Before the diagnosis or index year. [c]Mother or sister. [d]Exposed jobs included work in dry cleaning, chemical processing and manufacturing, metal degreasing and cleaning, and textile and electrical transformer manufacturing. [e]While living at their Cape Cod residence(s).

assumed to be unidirectional, and all houses were assumed to draw the same amount of water during a subject's residency.

To implement the Webler-Brown model, the locations, installation dates, and diameters of the VL/AC pipes in all public water supply systems in the study area were determined from maps provided by the local water suppliers or the Massachusetts DEP. Next, the public water distribution system data were digitized using geographic information system (GIS) mapping software (ArcView GIS, Environmental Systems Research Institute, Inc., Redlands, CA). GIS software was also used to geocode all subjects' Cape Cod residences to the parcel level. These data were linked to produce maps with spatial information on the parcel addresses and street locations of the subjects together with information on the water pipe configurations and attributes, including length, diameter, installation year, and composition (VL/AC or not). All residences located on a street with VL/AC pipe or on a street downstream from a VL/AC pipe were set aside for a detailed exposure assessment.

The exposure assessments involved making a judgment about the water flow direction and the load distribution because this information was not provided by the water companies. The water flow direction was determined by examining the water source locations and pipe sizes. The load distribution was determined by judging the point where residences connected to water mains. A protocol was designed so that all judgments were made in a consistent manner. All exposure assessments were performed by a single individual who was unaware of the subject's disease status. Intraobserver agreement was examined by performing 25 assessments twice several months apart, and interobserver agreement was tested by having another individual reevaluate 45% of the assessments. The levels of both intra- and interobserver agreement were excellent (Spearman correlation coefficients = 0.98 and 0.96, respectively; $p = 0.0001$).

Data analysis. First, ever-exposed versus never-exposed women were compared. Next, women with low and high cumulative RDDs were compared with never-exposed women. A low RDD was defined as an exposure level up to and including median cumulative RDD among exposed controls. Three successive categories of high exposure were also defined: above the 50th percentile, above the 75th percentile, and above the 90th percentile.

The empirical latent period, which is composed of both the induction and latent period, is the interval between the causal action of PCE and the diagnosis date or index year (Rothman 1981). Because it is not known if PCE might act as an early, intermediate, or late causal component, the analysis considered a range of empirical latent periods: 0, 5, 7, 9, 11, 13, 15, 17, and 19 years.

Women were considered exposed if they had at least one exposed residence during the relevant time period. RDDs were summed over all exposed addresses. The cumulative exposure was determined for each empirical latent period assumption. For example, only cumulative exposure that occurred more than 15 years before the diagnosis or index year was counted when a 15-year empirical latent period was assumed.

The exposure odds ratio (OR) was used to estimate the strength of the relationship between PCE exposure and the occurrence of breast cancer. The potential modifying effects of bathing habits, bottled water and water filter use were examined in stratified analyses. Ninety-five percent profile likelihood confidence intervals were used to indicate the precision of the crude associations (SAS 1994).

Multiple logistic regression was used to control simultaneously for potential confounding variables (Rosner 2000). The antilog of the beta coefficient of the exposure variable was used to estimate the OR. Adjusted analyses were conducted only for contrasts with at least three exposed cases and three exposed controls. A group of core confounders was controlled in all regression analyses: age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of prior breast cancer (before the current diagnosis or index year), age at first live birth or stillbirth, and occupational exposure to PCE. Additional potential confounders were added to the logistic regression models along with the core confounders, including history of benign breast disease; past use of diethylstilbestrol, oral contraceptives, and menopausal hormones; cigarette smoking history; alcohol drinking history; history of ionizing radiation treatment; quetelet index (measure of obesity); race; marital status; religion; educational level; and physical activity level. None of these additional variables changed the adjusted estimates by more than 10%, and so the final model included only the core confounders. We calculated 95% confidence intervals (95% CIs) for the adjusted ORs using maximum likelihood estimates of the standard errors (Rosner 2000).

Table 3. PCE exposure history of breast cancer cases and controls, crude[a] and adjusted[b] ORs, and 95% CIs.

Latency period (years)	PCE-exposed cases ($n = 672$)	PCE-exposed controls ($n = 616$)	Crude OR (95% CI)	Adjusted OR (95% CI)
0	155	136	1.1 (0.8–1.4)	1.1 (0.8–1.4)
5	129	107	1.1 (0.8–1.5)	1.2 (0.9–1.6)
7	111	96	1.1 (0.8–1.4)	1.1 (0.8–1.5)
9	97	85	1.1 (0.8–1.5)	1.1 (0.8–1.5)
11	79	65	1.1 (0.8–1.6)	1.2 (0.8–1.7)
13	61	45	1.3 (0.8–1.9)	1.3 (0.9–2.0)
15	44	31	1.3 (0.8–2.1)	1.4 (0.9–2.3)
17	21	21	0.9 (0.5–1.7)	1.0 (0.6–2.0)
19	9	9	0.9 (0.4–2.4)	1.1 (0.4–2.9)

[a]The OR was calculated relative to never-exposed cases ($n = 517$) and controls ($n = 480$). [b]Controlled for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth or stillbirth, and occupational exposure to PCE.

Table 4. Distribution of cumulative RDDs among PCE-exposed controls according to latency period for the present study only and for prior and present studies combined.

Latency period (years)	Minimum	Maximum	Median	75th percentile	90th percentile
Present study					
0	0.001	243.8	2.5	12.1	29.2
5	0.02	243.2	4.0	14.2	38.0
7	0.05	242.1	4.6	14.4	37.9
9	0.03	239.4	5.9	14.4	35.0
11	0.1	233.0	6.3	13.9	37.3
13	0.1	217.5	10.2	16.9	36.8
15	0.6	200.6	10.3	18.3	33.9
17	1.3	191.6	8.2	21.5	40.6
19	2.6	169.6	13.6	19.8	169.6
Present and prior studies combined					
0	0.001	243.8	3.6	15.5	41.8
5	0.02	243.2	6.9	17.6	41.7
7	0.05	242.1	6.9	18.2	40.9
9	0.03	239.4	6.4	16.5	38.4
11	0.1	233.0	6.8	18.5	37.3
13	0.1	217.5	10.3	18.9	36.8
15	0.6	200.6	10.3	18.3	49.1
17	1.3	191.6	8.2	21.5	40.6
19	2.6	169.6	13.6	19.8	169.9

Analyses were conducted among the present study population and among the present and prior study populations combined. Subject selection and data collection methods for the two studies were alike (Aschengrau et al. 1998). Although subjects in the prior study were permanent residents of fewer Cape Cod towns (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich) during an earlier period (1983–1986), the demographic characteristics and history of breast cancer risk factors were similar in the two populations.

The two studies also had similar exposure assessment methods (Aschengrau et al. 1998). The major differences were that the assessments for the present study used GIS software instead of tax assessor maps, had new information on some additional VL/AC pipe locations, and considered as exposed residences adjacent to and downstream from VL/AC pipe. (The prior study considered as exposed only residences adjacent to VL/AC pipe.) These differences contributed to the higher exposure prevalence in the present study. Adjusted analyses of the combined data took this difference into account by controlling for the study in which the subject was enrolled.

Results

The study subjects were predominantly white, ≥ 60 years of age, educated ≥ 12 years, and postmenopausal at diagnosis or index year (Table 2). Consistent with the literature, more cases than controls had a first-degree family history of breast cancer and prior benign breast disease and were either nulliparous or had a late age at first birth. A similar proportion of cases and controls had occupational exposure to PCE and had ever lived near a dry cleaner. Water use patterns, including bathing habits, the use of bottled water, and the use of water treatment devices, were also similar.

Overall, 23.1% of cases (n = 155) and 22.1% of controls (n = 136) were considered ever exposed to PCE-contaminated drinking water when latency was ignored, and from 1.3% (19 years' latency) to 19.2% (5 years' latency) of cases and from 1.5% (19 years' latency) to 17.3% (5 years' latency) of controls were considered ever exposed when latency was considered (Table 3). When latency was ignored, the RDD estimates obtained from the Webler-Brown model ranged from 0.001 to 243.8 among exposed controls, and the estimates at the median, 75th, and 90th percentile were 2.5, 12.1, and 29.2, respectively (Table 4). The minimum RDD increased and the maximum RDD decreased as more years of latency were considered. In addition, the cutoffs for median and the 75th percentile increased, whereas the cutoffs for the 90th percentile remained relatively stable as more years of latency were assumed.

No increases or small increases in the crude OR for breast cancer were seen among ever-exposed women either when latency was considered or when it was ignored (ORs, 0.5–1.3; Table 3). The ORs changed only slightly when confounding variables were controlled using logistic regression models (ORs, 1.0–1.4).

When the RDD was dichotomized at the median, no increases or small increases were seen in the crude and adjusted ORs for exposure levels below and above the median when latency was taken into account and when it was ignored (Table 5). However, small to moderate elevations in the crude and adjusted ORs were seen among women whose exposure

Table 5. Crude[a] (COR) and adjusted[b] ORs (AOR) for breast cancer according to various PCE exposure levels in the present study.

Latency period (years)	PCE exposure level			
	≤ Median	> Median	> 75th Percentile	> 90th Percentile
0				
Case/control (n)	68/68	87/68	52/34	28/13
COR (95% CI)	0.9 (0.6–1.3)	1.2 (0.8–1.7)	1.4 (0.9–2.2)	2.0 (1.0–3.9)
AOR (95% CI)	0.9 (0.7–1.4)	1.2 (0.9–1.7)	1.5 (1.0–2.4)	2.2 (1.1–4.3)
5				
Case/control (n)	58/54	71/53	43/26	14/10
COR (95% CI)	1.0 (0.7–1.5)	1.2 (0.9–1.8)	1.5 (0.9–2.5)	1.3 (0.6–3.0)
AOR (95% CI)	1.1 (0.7–1.6)	1.3 (0.9–1.9)	1.6 (1.0–2.7)	1.3 (0.5–3.0)
7				
Case/control (n)	42/48	69/48	41/24	14/9
COR (95% CI)	0.8 (0.5–1.3)	1.3 (0.9–2.0)	1.6 (0.9–2.7)	1.4 (0.6–3.4)
AOR (95% CI)	0.8 (0.5–1.3)	1.4 (0.9–2.1)	1.7 (1.0–2.9)	1.4 (0.6–3.4)
9				
Case/control (n)	42/43	55/42	36/21	15/8
COR (95% CI)	0.9 (0.6–1.4)	1.2 (0.8–1.9)	1.6 (0.9–2.8)	1.7 (0.7–4.1)
AOR (95% CI)	1.0 (0.6–1.5)	1.3 (0.8–2.0)	1.7 (1.0–3.0)	1.8 (0.8–4.4)
11				
Case/control (n)	36/33	43/32	30/16	11/6
COR (95% CI)	1.0 (0.6–1.7)	1.2 (0.8–2.0)	1.7 (0.9–3.2)	1.7 (0.6–4.6)
AOR (95% CI)	1.1 (0.6–1.7)	1.3 (0.8–2.2)	1.9 (1.0–3.5)	1.6 (0.6–4.5)
13				
Case/control (n)	32/23	29/22	19/11	8/4
COR (95% CI)	1.3 (0.7–2.2)	1.2 (0.7–2.2)	1.6 (0.8–3.4)	1.9 (0.6–6.2)
AOR (95% CI)	1.4 (0.8–2.4)	1.3 (0.7–2.4)	1.7 (0.8–3.7)	1.9 (0.6–6.6)
15				
Case/control (n)	26/16	18/15	12/7	8/3
COR (95% CI)	1.5 (0.8–2.8)	1.1 (0.6–2.2)	1.6 (0.6–4.1)	2.5 (0.7–9.4)
AOR (95% CI)	1.6 (0.9–3.1)	1.2 (0.6–2.4)	1.8 (0.7–4.8)	2.8 (0.7–11.0)
17				
Case/control (n)	11/11	10/10	4/5	1/2
COR (95% CI)	0.9 (0.4–2.2)	0.9 (0.4–2.3)	0.7 (0.2–2.8)	0.5 (0.0–5.1)
AOR (95% CI)	1.0 (0.4–2.5)	1.1 (0.4–2.6)	0.9 (0.2–3.5)	—[c]
19				
Case/control (n)	6/5	3/4	2/2	0/0
COR (95% CI)	1.1 (0.3–3.7)	0.7 (0.2–3.1)	0.9 (0.1–6.6)	0.0 (—)
AOR (95% CI)	1.3 (0.4–4.4)	0.8 (0.2–3.9)	—[c]	—[c]

[a]The OR was calculated relative to never-exposed cases (n = 517) and controls (n = 480). [b]Controlled for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth or stillbirth, and occupational exposure to PCE. [c]Adjusted analyses were not performed if there were fewer than three exposed cases and three exposed controls.

Table 6. PCE exposure history of breast cancer cases and controls, including crude[a] and adjusted[b] ORs (95% CIs) of combined data from previous and present studies.

Latency period (years)	PCE-exposed cases (n = 930)	PCE-exposed controls (n = 1,302)	Crude OR (95% CI)	Adjusted OR (95% CI)
0	191	217	1.3 (1.0–1.6)	1.1 (0.9–1.4)
5	154	163	1.4 (1.1–1.8)	1.2 (0.9–1.5)
7	128	135	1.4 (1.1–1.8)	1.1 (0.8–1.5)
9	111	110	1.5 (1.1–2.0)	1.2 (0.9–1.6)
11	86	83	1.5 (1.1–2.1)	1.1 (0.8–1.6)
13	65	52	1.8 (1.3–2.7)	1.3 (0.9–2.0)
15	44	35	1.8 (1.2–2.9)	1.3 (0.8–2.1)
17	21	21	1.5 (0.8–2.7)	1.0 (0.5–1.9)
19	9	9	1.5 (0.6–3.7)	1.1 (0.4–2.9)

[a]The OR was calculated relative to never-exposed cases (n = 739) and controls (n = 1,085). [b]Controlled for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth or stillbirth, occupational exposure to PCE, and study of origin (present or prior).

levels were above the 75th percentile when 0–15 years of latency were taken into account (crude ORs, 1.4–1.7; adjusted ORs, 1.5–1.9). A similar pattern was seen among women whose exposure levels were above the 90th percentile: there were small to moderate increases in the ORs when 0–15 years of latency were taken into account (crude ORs, 1.3–2.5; adjusted ORs, 1.3–2.8). The number of subjects whose exposure level was above the 75th and 90th percentiles was too small to provide meaningful results when more than 15 years of latency was taken into account.

Few changes in these findings were seen when the analyses were limited to postmenopausal women (adjusted ORs, 1.6–1.9 and 1.4–2.6 for exposure levels > 75th and > 90th percentiles, respectively). In addition, stratified analyses of ever-exposed women did not reveal any effect modification by bottled water use. However, ever-exposed subjects who took only baths at their exposed residence consistently had a reduced risk of breast cancer (ORs, 0.7–0.8 for 0–15 years of latency) compared with those who took only showers (ORs, 0.9–1.3 for 0–15 years of latency) and those who took a combination of baths and showers (ORs, 1.0–3.3). In addition, ever-exposed subjects who used a water treatment device at their exposed residence consistently had a reduced risk of breast cancer (ORs, 0.6–0.9 for 0–15 years of latency). The precision of the latter estimates was low because of the small proportion of cases and controls who used water treatment devices (12.9% and 13.7%, respectively; Table 2).

When the data from the present and previous studies were combined, small to moderate increases in the crude OR were seen among ever-exposed subjects when 0–19 years of latency were considered (ORs, 1.3–1.8; Table 6). However, the ORs were reduced when confounding variables were controlled (ORs, 1.0–1.3; Table 6).

In addition, no increases or modest increases in the crude and adjusted ORs were seen in the combined data when the exposure levels were dichotomized at the median (adjusted ORs, 0.9–1.5; Table 7). However, moderate increases in the ORs were seen among women whose exposure levels were above the 75th percentile when 0–15 years of latency were taken into account (adjusted ORs, 1.6–1.9). Several of these ORs were statistically significant.

Increases in the ORs were also observed among women whose exposure levels were above the 90th percentile when 0–15 years of latency were considered; these increases were generally smaller or equal to those observed at the 75th percentile (adjusted ORs, 1.3–1.9). The cutoffs for the 75th and 90th percentiles in the combined data were similar or higher than those in the present study (Table 4). Little or no change in these findings was seen when the combined analyses were limited to postmenopausal women (adjusted ORs, 1.4–2.0 and 1.3–2.2 for exposure levels > 75th and > 90th percentiles, respectively).

When the combined data were stratified according to bottled water use, the relative risks among ever-exposed women who did not consume bottled water were slightly higher (ORs, 1.2–2.1 for 0–17 years' latency) than among those who did consume bottled water (ORs, 0.8–1.4 for 0–17 years' latency). We were unable to examine the impact of bathing habits and water treatment devices in the combined data because of differences in the data collection instruments.

Table 7. Crude[a] (COR) and adjusted[b] (AOR) ORs for breast cancer according to various PCE exposure levels: combined data from present and previous studies.

Latency period (years)	PCE exposure level			
	≤ Median	> Median	> 75th percentile	> 90th percentile
0				
Case/control (*n*)	91/109	100/108	59/54	18/21
COR (95% CI)	1.2 (0.9–1.6)	1.4 (1.0–1.8)	1.6 (1.1–2.3)	1.3 (0.7–2.4)
AOR (95% CI)	1.0 (0.7–1.3)	1.2 (0.9–1.7)	1.6 (1.1–2.4)	1.3 (0.7–2.6)
5				
Case/control (*n*)	79/82	75/81	50/40	17/16
COR (95% CI)	1.4 (1.0–2.0)	1.4 (1.0–1.9)	1.8 (1.2–2.8)	1.6 (0.8–3.1)
AOR (95% CI)	1.1 (0.8–1.5)	1.3 (0.9–1.8)	1.6 (1.0–2.6)	1.5 (0.7–3.0)
7				
Case/control (*n*)	59/68	69/67	46/33	17/13
COR (95% CI)	1.3 (0.9–1.8)	1.5 (1.1–2.1)	2.0 (1.3–3.2)	1.9 (0.9–4.0)
AOR (95% CI)	0.9 (0.6–1.3)	1.3 (0.9–1.9)	1.8 (1.1–2.9)	1.7 (0.8–3.6)
9				
Case/control (*n*)	48/55	63/55	40/27	16/11
COR (95% CI)	1.3 (0.9–1.9)	1.7 (1.2–2.4)	2.2 (1.3–3.6)	2.1 (1.0–4.6)
AOR (95% CI)	0.9 (0.6–1.4)	1.4 (0.9–2.0)	1.9 (1.1–3.2)	1.9 (0.8–4.4)
11				
Case/control (*n*)	39/42	47/41	29/20	12/8
COR (95% CI)	1.4 (0.9–2.1)	1.7 (1.1–2.6)	2.1 (1.2–3.8)	2.2 (0.9–5.4)
AOR (95% CI)	1.0 (0.6–1.5)	1.4 (0.9–2.1)	1.8 (1.0–3.3)	1.8 (0.7–4.8)
13				
Case/control (*n*)	35/26	30/26	17/13	8/5
COR (95% CI)	2.0 (1.2–3.3)	1.7 (1.0–2.9)	1.9 (0.9–4.0)	2.3 (0.8–7.2)
AOR (95% CI)	1.4 (0.8–2.3)	1.3 (0.8–2.3)	1.6 (0.7–3.5)	1.7 (0.5–5.2)
15				
Case/control (*n*)	26/18	18/17	12/8	2/3
COR (95% CI)	2.1 (1.2–3.9)	1.6 (0.8–3.0)	2.2 (0.9–5.4)	1.0 (0.2–5.9)
AOR (95% CI)	1.5 (0.8–2.8)	1.1 (0.6–2.3)	1.7 (0.7–4.3)	—[c]
17				
Case/control (*n*)	11/11	10/10	4/5	1/2
COR (95% CI)	1.5 (0.6–3.4)	1.5 (0.6–3.5)	1.2 (0.3–4.4)	0.7 (0.1–8.1)
AOR (95% CI)	1.0 (0.4–2.4)	1.0 (0.4–2.6)	0.9 (0.2–3.4)	—[c]
19				
Case/control (*n*)	6/5	3/4	2/2	0/0
COR (95% CI)	1.8 (0.5–5.8)	1.1 (0.2–4.9)	1.5 (0.2–10.4)	0.0 (—)
AOR (95% CI)	1.3 (0.4–4.2)	0.9 (0.2–4.1)	—[c]	—[c]

[a]The OR was calculated relative to never-exposed cases (n = 739) and controls (n = 1,085). [b]Controlled for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth or stillbirth, occupational exposure to PCE, and study of origin (present or prior). [c]Adjusted analyses were not performed if there were fewer than three exposed cases and three exposed controls.

Discussion

The results of the present study and those of the prior and present studies combined suggest that women with the highest RDDs of PCE-contaminated drinking water have small to moderate increases in the risk of breast cancer compared with unexposed women (adjusted ORs from combined data, 1.6–1.9 for > 75th percentile and 1.3–1.9 for > 90th percentile). The magnitudes of the findings for the two highest exposure levels are similar; however, the precision of the estimates for exposure levels > 75th percentile are greater than those for exposure levels > 90th percentile. No meaningful increases in risk were observed at lower RDDs. Stratified analyses did not reveal any effect modification by bottled water use or bathing habits but suggested that ever-exposed subjects who used a water treatment device had a reduced risk of breast cancer (ORs, 0.6–0.8 for 0–15 years of latency).

These results are likely affected by exposure misclassification because we used the Webler-Brown model to estimate the historical PCE exposures. Incorrect model assumptions or errors in determining the model's input variables would have led to errors in estimating the RDDs. We are currently conducting a validation study of the model by comparing the RDD estimates with actual PCE concentrations in water samples that

were taken in 1980 when the contamination on Cape Cod was first discovered. However, because the PCE exposure assessments were conducted blindly, we think that these errors are likely nondifferential, and so associations with the dichotomous exposure measure are likely biased toward the null. Associations involving multiple exposure levels may be biased either toward or away from the null.

The study results are unlikely to be affected by biased selection of cases and controls. Breast cancer cases were obtained from all incident cases reported to the Massachusetts Cancer Registry. Comparison with other state cancer registries indicates nearly complete reporting for this cancer site (Massachusetts Department of Public Health 1995). Follow-up and interview rates were similar for cases and controls as were available demographic characteristics of participants and nonparticipants.

The proportion of nonparticipants who lived on a street with VL/AC pipe at the diagnosis or index year was 14.2% (14.4% for cases and 13.9% for non-RDD controls). This is lower than the exposure prevalence among participants because it is based on only a single address instead of a 40-year residential history. However, it is unlikely that it biased the results because the exposure prevalence is nearly identical for nonparticipating cases and controls.

The study results are also unlikely to be affected by observation bias. Although the interviewers were not masked to the disease status of the subjects, the interview was highly structured; the questions were closed-ended, carefully written, and tested; and the staff was well trained in appropriate interview techniques. In addition, comparable information quality was achieved by selecting deceased controls who had proxy interviews in the same manner as deceased cases. Lastly, the PCE exposure assessments were conducted blindly and independently of the interview.

With respect to confounding, the variables age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer (before the current diagnosis), age at first live birth or stillbirth, and occupational exposure to PCE were controlled in all multivariate analyses. Many additional potential confounders were considered, but none changed the ORs by more than 10%. Residual confounding by unmeasured factors, including other environmental pollutants, is a possible but an improbable explanation for the findings because these factors would have to be relatively common, closely correlated with PCE exposure, and fairly strong risk factors for breast cancer in order to produce the observed increases in the ORs. However, we are currently conducting another population-based case–control study among female residents of all 15 Cape Cod towns in collaboration with Silent Spring Institute in order to investigate the risk of breast cancer associated with nonenvironmental and environmental exposures, and so it will be possible to assess directly the associations between PCE and other exposures in the future.

The International Agency for Cancer Research (IARC) has classified PCE as a probable human carcinogen on the basis of animal experiments and epidemiologic studies (IARC 1995). The National Toxicology Program (NTP) also classifies PCE as an agent reasonably anticipated to be carcinogenic to humans (NTP 2000). Oral administration has produced liver cancer in mice, and inhalation exposure has produced kidney cancer and leukemia in rats and liver cancer in mice [Mennear et al. 1986; National Cancer Institute (NCI) 1977]. Mammary tumors have not been observed in these species.

Most of the human evidence regarding the carcinogenicity of PCE comes from studies of dry cleaners and other occupationally exposed groups (e.g., Blair et al. 1990; Ruder et al. 2001). Although these studies suggest associations with several cancer sites, particularly esophageal, bladder, cervical, intestinal, and lung cancer and non-Hodgkin lymphoma, the findings for breast cancer, as summarized below, are mainly null.

Three proportional mortality studies of women employed as launderers and dry cleaners found a deficit of breast cancer deaths (Duh and Asal 1984; Katz and Jowett 1981; Walker et al. 1997). The largest of these studies (n = 8,163 deaths) found a 9% decreased proportion of breast cancer deaths among white women and a 37% decreased proportion in black women (Walker et al. 1997). Interestingly, there were several cases of male breast cancer, and although substantially more than expected, the numbers were too small to produce stable effect estimates. These employees were combined laundry and dry cleaning workers, and so many were not exposed to PCE.

Cohort studies of mortality among dry cleaning workers primarily exposed to PCE have also reported no increases in breast cancer deaths. A National Institute for Occupational Safety and Health cohort study (n = 1,111 women) found a deficit of breast cancer deaths among all women employed in dry cleaning shops [standardized mortality ratio (SMR), 0.91; 95% CI, 0.55–1.40] and among the subgroup of workers exposed only to PCE (SMR, 0.78; 95% CI, 0.28–1.69) (Ruder et al. 2001). A National Cancer Institute mortality study of dry cleaning union members (n = 4,046 women) also found no increase in the risk of breast cancer death (SMR, 1.0; 95% CI, 0.7–1.4) (Blair et al. 1990). Lastly, a study of mortality among aircraft manufacturing workers found a small but statistically unstable increase in the breast cancer mortality among female workers who were routinely exposed to PCE (SMR, 1.16; 95% CI, 0.32–2.97) (Boice et al. 1999).

The results of two cancer incidence studies are both null for breast cancer. A large cohort study from Denmark, Norway, Sweden, and Finland found an 11% decreased incidence of breast cancer among female launderers and dry cleaners [n = 23,714; standardized incidence ratio (SIR), 89; 95% CI, 83–97] (Andersen et al. 1999). An unknown proportion were exposed to PCE. In addition, a population-based study in the Portland, Oregon–Vancouver, British Columbia, Canada, area found a lower breast cancer incidence rate among women working in laundry and dry cleaning jobs compared with that among all women (age-standardized rates, 77.4 vs. 100.3 per 100,000 person-years, respectively) (Morton 1995).

In contrast, a Canadian case–control study found a 4.9-fold increased risk of breast cancer among postmenopausal women usually employed in laundry and dry cleaning (95% CI, 1.3–18.7) (Band et al. 2000). This study was unusual because it controlled for the well-established breast cancer risk factors. In addition, a proportional mortality ratio (PMR) study found a statistically significant excess of breast cancer in male dry cleaning and laundry workers [PMR = 1,275 in white men (n = 4) and PMR = 1,587 in black men (n = 2)] (Walker et al. 1997).

Studies of workers exposed to trichloroethylene (TCE) are also relevant to the interpretation of our findings because TCE and PCE are closely related chlorinated ethylenes and share a similar toxicology (IARC 1995). A retrospective cohort study of aircraft maintenance workers (n = 3,717 women) found a 1.8-fold increase in the breast cancer mortality rate (95% CI, 0.9–3.3) among women who were mainly exposed to TCE compared with those with no chemical exposure (Blair et al. 1998). Another study of aircraft maintenance workers found a 1.3-fold increase in the breast cancer mortality rate among women routinely exposed to TCE (n = 192; 95% CI, 0.5–2.7) (Boice et al. 1999). In contrast, a Finnish cohort study of workers who had been biologically monitored for TCE, PCE, and tricholoroethane found a decreased incidence of breast cancer among women (n = 1,924) exposed to any of these halogenated hydrocarbons (SIR, 0.84; 95% CI, 0.44–1.48) (Anttila et al. 1995). Two mortality studies of aircraft manufacturing workers exposed to TCE also found decreased breast cancer death rates [SMR, 0.91; 95% CI, 0.52–1.48 (Garabrant et al. 1998); SMR, 0.75; 95% CI, 0.55–1.00 (Morgan et al. 1998)].

Most of these occupational studies have a number of limitations that likely reduce their

ability to detect an association with breast cancer. First, they suffer from exposure misclassification, stemming mainly from the use of broad job titles to classify individuals, and grouping together workers with a variety of chemical exposures. Second, most of the studies included a relatively small number of female subjects and so have low statistical power to detect small to moderate associations. Third, competing causes of death may account for the unelevated rates of breast cancer observed in the mortality studies.

Lastly, almost all of the occupational studies are missing information on key breast cancer confounders, such as age at first birth, family history of breast cancer, and socioeconomic status. In particular, because most women employed in dry cleaning and laundering jobs are from low socioeconomic classes, their baseline risk of breast cancer is lower than that of the general population (Kelsey 1993). Supporting evidence comes from a study of breast cancer incidence by major occupational groups that found a 33% lower incidence among blue-collar workers than among white-collar workers (Morton 1995). Thus, it is quite likely that the occupational studies with a general population comparison group are biased toward the null because of residual confounding by socioeconomic status.

Recently, Labreche and Goldberg (1997) described a hypothesis that lipophilic solvents like PCE can accumulate in breast tissue and have carcinogenic properties by acting either directly as genotoxic agents or indirectly through their metabolites. Although there are currently few epidemiologic studies on a relationship with breast cancer, either pro or con, this direction of research should be pursued in order to identify preventable causes of this common form of cancer.

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