

Tetrachloroethylene-contaminated Drinking Water in Massachusetts and the Risk of Colon–Rectum, Lung, and Other Cancers

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We conducted a population-based case-control study to evaluate the relationship between cancer of the colon-rectum ($n = 326$), lung ($n = 252$), brain ($n = 37$), and pancreas ($n = 37$), and exposure to tetrachloroethylene (PCE) from public drinking water. Subjects were exposed to PCE when it leached from the vinyl lining of drinking-water distribution pipes. Relative delivered dose of PCE was estimated using a model that took into account residential location, years of residence, water flow, and pipe characteristics. Adjusted odds ratios (ORs) for lung cancer were moderately elevated among subjects whose exposure level was above the 90th percentile whether or not a latent period was assumed [ORs and 95% confidence intervals (CIs), 3.7 (1.0–11.7), 3.3 (0.6–13.4), 6.2 (1.1–31.6), and 19.3 (2.5–141.7) for 0, 5, 7, and 9 years of latency, respectively]. The adjusted ORs for colon-rectum cancer were modestly elevated among ever-exposed subjects as more years of latency were assumed [OR and CI, 1.7 (0.8–3.8) and 2.0 (0.6–5.8) for 11 and 13 years of latency, respectively]. These elevated ORs stemmed mainly from associations with rectal cancer. Adjusted ORs for rectal cancer among ever-exposed subjects were more elevated [OR and CI, 2.6 (0.8–6.7) and 3.1 (0.7–10.9) for 11 and 13 years of latency, respectively] than were corresponding estimates for colon cancer [OR and CI, 1.3 (0.5–3.5) and 1.5 (0.3–5.8) for 11 and 13 years of latency, respectively]. These results provide evidence for an association between PCE-contaminated public drinking water and cancer of the lung and, possibly, cancer of the colon-rectum. **Key words:** cancer, drinking water, pollution, tetrachloroethylene. *Environ Health Perspect* 107:265–271 (1999). [Online 5 March 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p265-271paulu/abstract.html>

In 1976 the EPA discovered high levels (800–2,000 $\mu\text{g/l}$) of tetrachloroethylene [or perchloroethylene (PCE)] in some samples of drinking water in Rhode Island. The samples were taken for routine trihalomethane monitoring. No specific source of contamination was apparent, but the affected taps were closed (1). Two years later, high levels of PCE-contaminated drinking water were found in another area of Rhode Island. The only feature common to both incidents was the use of recently installed asbestos cement (AC) pipes with vinyl liners (VLs). By the end of 1979, the EPA determined conclusively that the VL was the source of the PCE contamination, and began notifying state officials in locations where similar pipes had been installed (1).

The vinyl lined AC pipes had been introduced in the six New England states in the late 1960s to counter acidity problems. Upon receipt of an order, the manufacturer hand-sprayed two coats of a slurry of vinyl toluene resin (Johns-Manville, Denver, CO) and the solvent PCE to the inner surface of the pipe. Pipes were allowed to dry for 48 hr and then shipped to the installation site (2). Because of its volatility, it was assumed that the PCE would evaporate before the pipe was used. Although some installers noted that the pipe was wet upon its arrival (3), more than a decade elapsed before anyone realized that considerable

quantities of PCE had remained and were slowly leaching into the drinking water.

After this discovery, an investigation in Massachusetts turned up approximately 660 m of VL/AC pipes, much of it installed in five towns of the upper Cape Cod area (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich) (4). VL/AC pipes with low water flow had the highest PCE concentrations (some measurements were as high as 18,000 $\mu\text{g/l}$ at dead-end sites in Falmouth) (5). In the early 1980s the Massachusetts Department of Environmental Protection instituted a program of flushing and bleeding to reduce concentrations below 40 $\mu\text{g/l}$, a level derived from the EPA suggested no adverse response level at the time, but by that time thousands of residents had been exposed to PCE-contaminated water during the previous decade.

Several years after the PCE contamination was discovered, the Massachusetts Department of Public Health reported elevations in cancer mortality, particularly lung cancer and leukemia, in the upper Cape Cod area as compared to statewide averages (6). When statewide cancer surveillance began in 1982, statistically significant excesses were also seen in the incidence of cancer of the breast, colon-rectum, lung, and blood-forming organs, and statistically unstable increases were seen for cancer of the pancreas, kidney, and bladder in at least

one of the upper Cape towns as compared to the entire state (7).

In response to substantial concern from local citizens' groups, we undertook a set of population-based case-control studies to evaluate the relationship between nine types of cancer (lung, breast, colon-rectum, bladder, kidney, pancreas, brain, and liver cancer, and leukemia) and a number of environmental exposures, including PCE exposure from public drinking water, in the upper Cape Cod region (8,9). These cancer sites were selected because their rates were elevated in at least one upper Cape town and/or because of community interest.

Our first investigation of PCE-contaminated drinking water investigated bladder and kidney cancer and leukemia (10). We found an increased risk of leukemia, whether or not the latent period was taken into account, and an increased risk of bladder cancer when the latent period was ignored. Both effects were greatest among subjects whose exposure level was above the 90th percentile. Subsequently, we undertook another study to examine exposure to PCE-contaminated water in relation to the remaining six cancer sites studied in the original case-control investigation. The breast cancer analysis has been previously published (11). Although we also found an increased risk of breast cancer for highly exposed women, firm conclusions were limited by the small number of exposed subjects. The current paper presents the methods and results for cancer of the colon-rectum, lung, brain, and pancreas. Liver cancer was not included because there were too few cases ($n = 4$) for meaningful evaluation.

Materials and Methods

Selection and enrollment of study population. The cases were incident cancers of the colon-rectum ($n = 420$), lung ($n = 326$), brain ($n = 42$), and pancreas ($n = 43$)

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diagnosed from 1983 through 1986 among permanent residents of the five upper Cape towns (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich) and reported to the Massachusetts Cancer Registry. The controls came from the same source population as the cases: permanent residents of the five upper Cape towns during 1983–1986. Because many cases were elderly or deceased at the start of the study, three sources were needed to identify comparable controls efficiently.

First, living controls 65 years and over were identified using lists of the elderly obtained from the Health Care Financing Administration (HCFA). These lists are estimated to include 95% of individuals aged 65 years and older in the United States (12). Using the HCFA roster, 611 controls were randomly selected from the upper Cape population using an age- and gender-stratified sampling scheme (Table 1). Second, controls who died since 1983 were randomly selected from a file of all upper Cape resident deaths furnished by the Massachusetts Department of Vital Statistics and Research. This listing included all individuals, regardless of the cause of death. A random sampling scheme stratified on age, gender, and year of death resulted in the selection of 918 deceased controls. Deceased controls were selected to approximately balance the proportion of proxy interviews completed by next-of-kin respondents in the case and control groups. Third, a random sample of living controls under 65 years of age who lived in the upper Cape towns during the case ascertainment period was obtained via random-digit dialing. At the time of the 1980 U.S. Census, more than 95% of Massachusetts housing units had telephone service (13). Of the 2,236 households identified using random-digit dialing, 249 eligible respondents were identified, of whom 184 were interviewed.

Follow-up and interviews. Current addresses and telephone numbers of subjects or their next of kin were determined using Cancer Registry, HCFA, physician, driver's license, and vital statistics records; voter registration lists; and telephone directories. After informed consent was obtained, trained personnel carried out structured interviews to gather information on demographic characteristics, smoking and alcohol consumption, medical conditions, reproductive events, occupations since 18 years of age, and a residential history from 1943 through 1986. This time interval encompassed the likely period for the initiation and development of the cancers under study.

A total of 79% of cases, 74% of eligible random-digit-dial controls, 76% of HCFA controls, and 79% of next-of-kin for

Table 1. Selection and enrollment of cancer cases and controls

	Selected	Excluded			Interviewed
		Never found or contacted	Not eligible	Doctor/subject refusal	
Cases (type of cancer)					
Colon-rectum	420	51	3	40	326
Lung	326	46	8	20	252
Brain	42	1	1	3	37
Pancreas	43	3	1	2	37
Controls					
HCFA	611	21	53	73	464
Deceased	918	97	27	71	723
Random-digit dial	2,236	456	1,531 ^a	65	184

HCFA, Health Care Financing Administration.

^aIncludes 129 individuals who refused to answer the eligibility screening questions.

deceased controls were interviewed (Table 1). Response rates were similar across cancer sites. Eighty-six percent of the completed interviews were conducted by telephone and the remainder were conducted in person.

The demographic characteristics of interviewed and noninterviewed cases and controls were similar. Of the noninterviewed cases, 96.5% were white, 80.3% were aged 60 years and older, 39.0% were male, and 44.0% were alive at the time of contact. By comparison, 94.7% of the noninterviewed HCFA and deceased controls were white, 89.5% were aged 60 years and older, 41.2% were male, and 43.5% were alive at the time of contact. No demographic information was available on noninterviewed random-digit-dial controls.

Site-specific control groups were chosen by first stratifying each case group on the basis of age, 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. Index years were then assigned randomly to controls to correspond to the diagnosis years of the cases. Assignments were weighted to achieve the same distribution as the corresponding case group's diagnosis years. Controls who moved to the upper Cape area after the index year (1.4–5.6%) and cases and controls with incomplete residential histories (2.7–4.6% of cases and 4.1–5.7% of controls) were excluded. The numbers of cases and controls in the final analyses are given in Table 2.

PCE exposure estimation. Exposure to PCE in drinking water was estimated using an algorithm developed by Webler and Brown (14). Webler and Brown defined the relative delivered dose (RDD) as the estimated mass of PCE (in milligrams) that entered a house as a drinking water solute over a specified period of time. They used the term "relative" to emphasize that the RDD is appropriately used for order-of-magnitude estimates of delivered dose rather than absolute quantification.

The Webler–Brown algorithm is based on a kinetic model for PCE leaching from VL pipe—a model that Demond proposed and tested in 1982 (2). The model makes the following assumptions: 1) a finite amount of PCE in the lining is distributed uniformly on the inside pipe surface; 2) the amount of PCE per unit length is the same for all pipes at the time of installation and to a first approximation does not change over time; 3) PCE leaching is far from equilibrium because water is always flowing; and 4) the leaching rate decreases with time because the diffusion coefficient for PCE decreases as the vinyl liner ages.

The rate at which the initial stock of PCE leaches depends on numerous factors, including physical parameters of the pipe, and the water temperature, density, viscosity, and flow rate. In the Webler–Brown model, a pipe's initial stock of PCE is estimated from its length and diameter and the leaching rate is estimated from the pipe's age.

Water flow rate is affected both by the geometry of the distribution network and the load (i.e., water demand) at each connection within the network. Webler and Brown simplified network geometry to four generic cases: dead-ends, circles, circles with taps, and in-line. Any actual pipe configuration was considered to be one or a combination of these geometries. The load on the pipes at any given time depends on the number of houses connected to it, the connection date, and the water consumption at each house. Water flow was assumed to be unidirectional and all houses were assumed to draw the same quantity of water.

To implement the Webler–Brown model, locations of VL/AC pipes in all public water supply systems in the area were determined. Five of the eleven water suppliers reported no VL/AC pipes in their districts. The remaining six suppliers provided water distribution maps indicating the location, diameters, and installation dates of the VL/AC pipes.

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

Characteristic	Colon-rectum		Lung		Brain		Pancreas	
	Cases (n = 311)	Controls (n = 1,158)	Cases (n = 243)	Controls (n = 1,206)	Cases (n = 36)	Controls (n = 703)	Cases (n = 36)	Controls (n = 622)
Female gender	46.3	56.1	42.0	57.0	47.2	57.6	63.9	61.4
White race	96.1	96.3	96.3	96.6	100.0	96.6	97.2	96.9
Age (years) ^a								
1–49	1.9	3.3	3.7	5.4	22.2	2.1	0.0	0.2
50–59	9.0	10.0	12.3	10.3	13.9	10.7	5.6	2.4
60–69	25.4	34.4	38.3	33.3	22.2	38.0	13.9	33.3
70–79	42.4	33.9	35.8	33.7	30.6	35.3	58.3	45.5
80+	21.2	18.4	9.9	17.4	11.1	13.9	22.2	18.7
Educational level ≥12 years	79.1	80.3	81.3	80.9	82.9	82.4	85.7	80.7
Alive at interview	54.7	46.9	17.7	46.8	22.2	37.7	5.6	36.2
Prior occupational exposure to solvents	20.6	23.9	35.5	24.7	20.0	24.0	8.3	21.1
Usual bathing habits								
Mostly showers	51.3	46.3	53.8	47.7	54.3	47.9	48.6	42.7
Mostly baths	31.9	35.8	26.7	33.9	20.0	34.9	37.1	37.5
About equal	16.8	17.9	19.5	18.4	25.7	17.2	14.3	19.8
Ever regularly drank bottled water	8.2	8.5	8.1	8.7	5.7	8.4	17.1	8.5
Ever regularly smoked cigarettes	60.7	63.9	93.4	65.3	63.9	68.4	50.0	65.3
History of colon disease ^b	44.6	13.5	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
Occupational history associated with:								
Colon-rectum cancer	8.0	7.2	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
Lung cancer	— ^c	— ^c	23.9	12.2	— ^c	— ^c	— ^c	— ^c

^aAge at diagnosis or index year.^bPolyps, inflammatory bowel disease, ulcerative colitis.^cNot a risk factor for this cancer site.

All subjects that resided on streets with VL/AC pipe were identified and located on the distribution network. For every residence on a VL/AC street, a schematic diagram was drawn depicting water flow. Pipe length, diameter, installation date, and the location and number of households (the load) were recorded. Data for these variables were entered into a database management system that checked for inconsistencies and calculated the RDD. All entered data were also proofread for accuracy.

Creating the schematic frequently involved judgment of water distribution characteristics beyond the data recorded on the water distribution maps. Water flow direction was determined by examining several features of the distribution network, including water source locations and pipe sizes. Maps of tax assessment parcels and the water distribution system were used to gauge the spacing of house connections on the pipes. A strict protocol was devised to make these decisions in a consistent manner. The individuals conducting the exposure assessments were unaware of who was a case and who was a control.

Data analysis. The interval between the causal action of an exposure and the eventual diagnosis of disease can be conceptually

divided into the induction period—the interval between the action of a cause and disease onset—and the latent period—the subsequent interval between disease onset and clinical diagnosis (15). We merged these two periods into the empirical latent period because the time of disease onset was not possible to determine. In addition, we considered a variety of empirical latent periods (0, 5, 7, 9, 11, 13, and 15 years) because the induction and latent periods appropriate to PCE exposure and the development of the cancers under study was unknown.

For each empirical latent period assumption, we calculated the cumulative exposure during the relevant time period. For instance, we counted the cumulative exposure that occurred more than 5 years before the diagnosis or index year when we assumed an empirical latent period of 5 years, and we counted exposures up to the diagnosis or index year when no empirical latent period was assumed.

Exposure was first examined as ever versus never exposed and then ever-exposed individuals were further divided into low and high cumulative RDDs. Low RDD was defined as a level up to and including the median (50th percentile) among the exposed. In addition, three overlapping

categories were defined to signify successively higher exposure levels: above the median, above the 75th percentile, and above the 90th percentile. Individuals were considered exposed if they had at least one exposed residence during the appropriate time period. If an individual had more than one exposed residence, RDDs were cumulated over all residences. The referent category always consisted of never-exposed subjects.

The crude analyses examined potential PCE exposure in relation to each cancer site and empirical latent period. When numbers were sufficient, separate analyses were conducted for colon and rectum cancers. The exposure odds ratio (OR) was used to estimate the strength of the association between PCE exposure and the cancer. The potential modifying effects of drinking bottled water and usual bathing habits were examined in stratified analyses. Reported bathing habits were categorized as taking mostly baths, mostly showers, and showers and baths in approximately equal frequency. Ninety-five percent profile likelihood confidence intervals (CIs) were computed to indicate the precision of the crude associations (16).

Multiple logistic regression was used to control simultaneously for potential confounding variables (17). The antilog of the β -coefficient of the exposure variable served as an estimate of the OR. Adjusted analyses were performed among the colon-rectum and lung cancer study populations only if there were at least three exposed cases and controls. Variables controlled in the colon-rectum and lung cancer analyses were as follows: age at diagnosis or index year; vital status at interview; sex; and occupational exposure to PCE, benzene, and other solvents. In addition, history of polyps, inflammatory bowel disease, or ulcerative colitis, and occupational history associated with colon-rectum cancer (e.g., jobs with asbestos or solvent exposure) were controlled in the colon-rectum cancer analyses. The usual number of cigarettes smoked and history of cigar or pipe use, living with a smoker, and occupational history associated with lung cancer (e.g., jobs with arsenic, asbestos, chromium, coal tar pitch exposure) were controlled in the lung cancer analyses. Ninety-five percent CIs for the adjusted ORs were computed based on the method of profile likelihood intervals (16). Because so few brain and pancreas cancer cases were considered exposed, no adjusted analyses were performed for these two cancer sites.

Results

Study population characteristics. The cases and controls were predominantly white, elderly, and educated 12 or more years (Table 2). A history of occupational exposure

to solvents was frequently reported by cases and controls (range 8.3–35.5%). Showering was the predominant form of bathing (range 42.7–54.3%), and regular bottled water use was infrequent (range 5.7–17.1%). The distributions of several cancer risk factors were as expected, with more cancer cases reporting a history of the characteristic than controls.

When the empirical latent period was ignored, the proportion of cancer cases that were classified as ever exposed to PCE-contaminated drinking water ranged from 8.3% (for brain and pancreas cancer) to 14.1% (for colon-rectum cancer) (Table 3). Approximately 13% of controls were considered ever exposed. The frequency of exposed subjects diminished rapidly as longer empirical latent periods were assumed.

When latency was ignored, the RDD estimates obtained from the Webber-Brown model among exposed colon-rectum cancer cases and controls ranged from 0.002 to 356.7, and estimates at the median, 75th, and 90th percentiles were 7.0, 21.4, and 46.1, respectively (Table 4). The range for exposed lung cancer cases and controls was 0.002–703.5 and the estimates at the median, 75th, and 90th percentile were 7.0, 25.7, and 49.4, respectively. The maximum RDD for both cancer sites decreased as more years of latency were taken into account; however, cutoffs for the median, 75th, and 90th percentiles were stable across most assumptions for the empirical latent period. With the exception of lower maximum levels, the RDD distributions for exposed brain and pancreas cancer cases and controls were similar to those of the other study populations (data not shown).

The crude OR for colon-rectum cancer was not elevated or negligibly elevated among ever-exposed subjects when short empirical latent periods were assumed (ORs 1.1, 1.1, 1.0, and 1.3 with 0–9 years of latency; Table 3). ORs were moderately increased when 11 and 13 years of latency were assumed (ORs 1.8 and 2.1, respectively), but fell when 15 years of latency were assumed and a single exposed case (of colon cancer) and five exposed controls remained (OR 0.8). When colon and rectum cancer cases were analyzed separately, the ORs were more elevated for rectal cancer. Crude ORs for rectal cancer were 0.8, 1.0, 1.1, 1.4, 2.4, and 3.0 when 0–13 years of latency were assumed, whereas those for colon cancer were 1.2, 1.2, 1.0, 1.2, 1.5, and 1.6 when 0–13 years of latency were taken into account.

The crude ORs for lung cancer among ever-exposed subjects exhibited a similar pattern—a moderately increased relative

Table 3. Perchloroethylene (PCE) exposure history of cases and controls, crude and adjusted odds ratios (ORs), and 95% confidence intervals (CIs)

Cancer type, empirical latent period (years)	No. PCE- exposed cases	No. PCE- exposed controls	Crude		Adjusted	
			OR	CI	OR	CI
Colon-rectum cancer						
0	44	153	1.1	0.8-1.5	1.1	0.7-1.5
5	29	98	1.1	0.7-1.7	1.0	0.6-1.6
7	19	71	1.0	0.6-1.7	0.9	0.5-1.6
9	16	46	1.3	0.7-2.3	1.3	0.7-2.3
11	11	23	1.8	0.8-3.7	1.7	0.8-3.8
13	6	11	2.1	0.7-5.4	2.0	0.6-5.8
15	1	5	0.8	0.0-4.7	— ^a	—
Lung cancer						
0	33	158	1.0	0.7-1.5	1.1	0.7-1.7
5	22	104	1.1	0.6-1.7	1.2	0.7-2.0
7	17	74	1.1	0.6-1.9	1.3	0.7-2.3
9	14	49	1.4	0.7-2.6	1.4	0.7-2.8
11	8	32	1.2	0.5-2.6	1.1	0.5-2.5
13	5	13	1.9	0.6-5.1	2.0	0.6-5.9
15	1	7	0.7	0.0-4.0	— ^a	—
Brain cancer						
0	3	92	0.6	0.1-1.7	— ^a	—
5	3	59	1.0	0.2-2.9	— ^a	—
7	2	43	0.9	0.1-3.0	— ^a	—
9	1	27	0.7	0.0-3.4	— ^a	—
11	0	14	0.0	—	—	—
13	0	7	0.0	—	—	—
15	0	5	0.0	—	—	—
Pancreas cancer						
0	3	81	0.6	0.1-1.7	— ^a	—
5	2	54	0.6	0.1-2.1	— ^a	—
7	0	36	0.0	—	—	—
9	0	23	0.0	—	—	—
11	0	9	0.0	—	—	—
13	0	4	0.0	—	—	—
15	0	0	0.0	—	—	—

^aAdjusted analyses were not conducted because the number of exposed cases and controls was too small.

Table 4. Distribution of cumulative relative delivered doses (RDDs) among perchloroethylene (PCE)-exposed subjects in colon-rectum and lung cancer analyses according to empirical latent period

Cancer type, empirical latent period (years)	No. exposed subjects	Min	Max	Median	75th percentile	90th percentile
Colon-rectum cancer						
0	197	0.002	356.7	7.0	21.4	46.1
5	127	0.11	219.8	8.3	26.4	43.9
7	90	0.07	166.4	8.0	20.5	45.1
9	62	0.07	154.3	7.2	18.2	34.0
11	34	0.36	139.0	7.5	23.0	39.5
13	17	0.18	124.1	9.5	24.2	32.9
15	6	2.98	88.0	12.0	21.2	81.3
Lung cancer						
0	191	0.002	703.5	7.0	25.6	49.4
5	126	0.07	625.6	9.6	25.2	52.2
7	91	0.12	500.4	9.0	25.5	49.7
9	63	0.15	385.1	7.8	26.6	45.7
11	40	0.18	187.6	8.9	25.4	36.8
13	18	0.62	133.2	6.8	23.5	28.3
15	8	1.56	110.0	12.0	17.7	83.4

Abbreviations: Min, minimum; max, maximum.

risk (OR 1.9) when 13 years of latency was assumed that declined when 15 years of latency was assumed and few exposed subjects remained (OR 0.7). No elevations in the crude ORs for brain and pancreas cancer were observed among ever-exposed subjects; however, only three brain and

pancreas cancer cases each were exposed when the empirical latent period was ignored and the number diminished as increasing empirical latent periods were applied. When conducted, adjustment for confounding variables did not appreciably alter the crude measures of associations for

Table 5. Perchloroethylene (PCE) exposure history, crude odds ratios (ORs), and 95% confidence intervals (CIs) according to various PCE exposure levels among subjects in colon-rectum and lung cancer analyses

Cancer type,	PCE exposure level															
Empirical	≤Median				>Median				>75th percentile				>90th percentile			
latent period (years)	Cases ^a	Controls ^a	OR	(CI)	Cases ^a	Controls ^a	OR	(CI)	Cases ^a	Controls ^a	OR	(CI)	Cases ^a	Controls ^a	OR	(CI)
Colon–rectum cancer																
0	23	75	1.2	(0.7–1.8)	21	78	1.0	(0.6–1.6)	8	41	0.7	(0.3–1.5)	5	15	1.3	(0.4–3.3)
5	16	47	1.3	(0.7–2.2)	13	51	1.0	(0.5–1.7)	6	26	0.9	(0.3–2.0)	5	8	2.4	(0.7–7.1)
7	6	39	0.6	(0.2–1.3)	13	32	1.5	(0.8–2.9)	4	18	0.8	(0.2–2.3)	3	6	1.9	(0.4–7.2)
9	6	25	0.9	(0.3–2.1)	10	21	1.8	(0.8–3.8)	2	13	0.6	(0.1–2.1)	2	4	1.9	(0.3–9.7)
11	6	11	2.1	(0.7–5.4)	5	12	1.6	(0.5–4.3)	2	6	1.3	(0.2–5.5)	1	2	1.9	(0.1–19.7)
13	4	4	3.8	(0.9–16.0)	2	7	1.1	(0.2–4.5)	1	3	1.3	(0.1–9.8)	1	1	3.8	(0.1–95.2)
15	1	2	1.9	(0.1–19.7)	0	3	0.0	(–)	0	1	0.0	(–)	0	1	0.0	(–)
Lung cancer																
0	17	78	1.1	(0.6–1.8)	16	80	1.0	(0.6–1.7)	11	37	1.5	(0.7–2.9)	5	14	1.8	(0.6–4.7)
5	9	54	0.8	(0.4–1.6)	13	50	1.3	(0.7–2.4)	6	25	1.2	(0.4–2.8)	3	10	1.5	(0.3–4.9)
7	6	39	0.8	(0.3–1.7)	11	35	1.6	(0.7–3.0)	5	18	1.4	(0.5–3.5)	3	6	2.5	(0.5–9.5)
9	5	26	1.0	(0.3–2.3)	9	23	2.0	(0.8–4.1)	4	11	1.8	(0.5–5.4)	3	3	5.0	(0.9–27.1)
11	3	17	0.9	(0.2–2.7)	5	15	1.7	(0.5–4.3)	2	8	1.2	(0.2–5.0)	1	3	1.7	(0.1–13.1)
13	3	6	2.5	(0.5–9.5)	2	7	1.4	(0.2–5.9)	0	4	0.0	(–)	0	2	0.0	(–)
15	1	3	1.7	(0.1–13.1)	0	4	0.0	(–)	0	2	0.0	(–)	0	1	0.0	(–)

^aValues are number exposed.**Table 6.** Adjusted^a odds ratios (ORs) for colon-rectum and lung cancer according to various perchloroethylene (PCE) exposure levels

Cancer type, empirical latent period (years)	PCE exposure level							
	≤Median		>Median		>75th percentile		>90th percentile	
	OR	(CI)	OR	(CI)	OR	(CI)	OR	(CI)
Colon-rectum cancer								
0	1.2	(0.7–1.9)	1.0	(0.6–1.6)	0.7	(0.3–1.6)	1.0	(0.3–2.8)
5	1.1	(0.6–2.0)	0.9	(0.4–1.7)	0.8	(0.3–1.9)	1.7	(0.5–5.7)
7	0.6	(0.2–1.3)	1.4	(0.7–2.9)	0.9	(0.2–2.5)	1.5	(0.3–6.1)
9	0.8	(0.3–2.0)	1.8	(0.8–4.1)	— ^b	—	— ^b	—
11	2.0	(0.6–5.8)	1.5	(0.4–4.4)	— ^b	—	— ^b	—
13	3.9	(0.8–17.8)	0.9	(0.1–4.6)	— ^b	—	— ^b	—
15	— ^b	—	— ^b	—	— ^b	—	— ^b	—
Lung cancer								
0	1.0	(0.5–1.7)	1.2	(0.7–2.2)	1.8	(0.8–3.9)	3.7	(1.0–11.7)
5	0.8	(0.4–1.7)	1.7	(0.8–3.4)	1.7	(0.6–4.5)	3.3	(0.6–13.4)
7	0.8	(0.3–1.9)	1.9	(0.9–4.1)	1.6	(0.5–4.4)	6.2	(1.1–31.6)
9	1.0	(0.3–2.6)	2.0	(0.8–4.7)	1.8	(0.5–6.0)	19.3	(2.5–141.7)
11	0.8	(0.2–2.6)	1.5	(0.5–4.4)	— ^b	—	— ^b	—
13	2.6	(0.5–11.6)	— ^b	—	— ^b	—	— ^b	—
15	— ^b	—	— ^b	—	— ^b	—	— ^b	—

^aSee text for confounders that were controlled.^bAdjusted analyses were not conducted because the number of exposed cases and controls was too small.

lung and colon-rectum cancer (Table 3). The adjusted ORs and 95% CIs for rectal cancer alone were 0.8 (0.4–1.5), 1.0 (0.5–2.0), 1.1 (0.4–2.3), 1.6 (0.6–3.6), 2.6 (0.8–6.7), and 3.1 (0.7–10.9) when 0–13 years of latency were assumed, whereas those for colon cancer were 1.2 (0.8–1.9), 1.1 (0.6–1.8), 0.9 (0.4–1.7), 1.2 (0.5–2.4), 1.3 (0.5–3.5), and 1.5 (0.3–5.8) when 0–13 years of latency were taken into account.

When the data were examined according to the degree of exposure, the crude ORs for colon-rectum cancer were moderately elevated for subjects whose exposure level was greater than the 90th percentile and when 5 or more years of latency was assumed (ORs 2.4, 1.9, 1.9, 1.9, and 3.8 for 5–13 years of latency; Table 5). Crude

ORs for colon-rectum cancer were variable for lower exposure levels; however, they tended to become elevated as more years of latency were considered. The number of exposed subjects was too small to examine the degree of exposure separately for colon and rectum cancer cases.

Crude ORs for lung cancer were moderately increased for subjects whose exposure was above the 90th percentile whether or not an empirical latent period was assumed (ORs 1.8, 1.5, 2.5, 5.0, and 1.7, for 0–11 years of latency; Table 5). Inconsistent increases were seen at lower exposure levels. Many of these estimates were unstable because of the small number of exposed subjects.

Adjustment for confounding variables did not appreciably change the ORs for

colon-rectum cancer among subjects with exposure levels below the 90th percentile; however, the adjusted ORs fell by 20–30% for subjects with an exposure level above the 90th percentile (adjusted ORs 1.0, 1.7, and 1.5, respectively, for 0, 5, and 7 years of latency; Table 6). Controlling for confounding did not substantially alter the crude ORs for lung cancer among subjects with exposure levels below the 90th percentile; however, the adjusted ORs were further increased among subjects with an exposure level above the 90th percentile (adjusted ORs 3.7, 3.3, 6.2, and 19.3 for 0–9 years of latency). Several confounders contributed to the increased ORs for lung cancer including gender, vital status at interview, and usual number of cigarettes smoked.

To investigate the potential modifying effects of bottled water use, analyses were conducted among subjects who reported never using bottled water (the number of subjects who reported using bottled water was too small to analyze separately). Associations between PCE exposure and cancer of the colon-rectum were closer to the null when the bottled water users were excluded. Crude ORs of colon-rectum cancer among nonbottled water users whose exposure level was above the 90th percentile were 1.0 (CI, 0.2–3.3), 1.9 (CI, 0.4–7.1), 1.5 (CI, 0.2–6.9), 1.9 (CI, 0.3–9.6), 1.9 (CI, 0.1–19.4), and 3.7 (CI, 0.1–93.7), respectively, when 0–13 years of latency were applied. Few adjusted ORs could be calculated because the number of exposed subjects was too small.

The pattern of associations between PCE exposure and lung cancer remained similar when bottled water users were excluded. The adjusted ORs for an exposure

level greater than the 90th percentile were 6.1 (CI, 1.4–23.6), 7.2 (CI, 1.2–34.2), 9.7 (CI, 1.5–53.5), 19.2 (CI, 2.5–140.0), and 5.0 (CI, 0.2–57.0) given 0, 5, 7, 9, and 11 years of latency, respectively.

When usual bathing habits were examined, the ORs for colon–rectum cancer were lower among ever-exposed subjects who reported taking mostly showers, and ORs were higher among ever-exposed subjects in the other bathing categories, particularly those who reported taking showers and baths about equally. Adjusted ORs for colon–rectum cancer among ever-exposed subjects who reported taking mostly baths were 1.6 (CI, 0.8–3.1), 1.2 (CI, 0.5–2.9), 1.1 (CI, 0.4–2.9), 1.7 (CI, 0.5–5.1), 2.3 (CI, 0.7–7.4), and 2.5 (CI, 0.4–12.4) given 0, 5, 7, 9, 11, and 13 years of latency, respectively, and they were 1.3 (CI, 0.5–3.5), 1.5 (CI, 0.5–4.6), 2.1 (CI, 0.6–6.7), 3.2 (CI, 0.8–11.9), and 8.5 (CI, 1.1–108.4), given 0, 5, 7, 9, and 11 years of latency, respectively, among ever-exposed subjects who reported taking baths and showers about equally.

The associations between PCE exposure and lung cancer were also somewhat modified by the subject's bathing habits. While the ORs among ever-exposed subjects who reported taking mostly baths and mostly showers were similar to the overall associations, the ORs were stronger among ever-exposed subjects who reported taking baths and showers about equally. The adjusted ORs were 1.9 (CI, 0.6–5.6), 2.4 (CI, 0.7–8.1), 2.5 (CI, 0.6–9.8), 2.6 (CI, 0.6–10.5), and 1.5 (CI, 0.2–8.7) given 0–11 years of latency.

Discussion

In this study, high cumulative exposure to PCE-contaminated drinking water at a level above the 90th percentile was associated with an increased risk of lung cancer and, possibly, colon–rectum cancer. Adjusted ORs for lung cancer were moderately elevated among subjects whose exposure was above the 90th percentile whether or not the latent period was taken into account. Adjusted ORs for colon–rectum cancer were not elevated among subjects whose exposure level was above the 90th percentile when no latency was assumed but were modestly elevated when 5 and 7 years of latency were assumed. Adjusted ORs for colon–rectum cancer, particularly rectal cancer, were also modestly elevated among ever-exposed subjects as increasing years of latency were taken into account.

These results should be interpreted cautiously because the precision of the associations was low, particularly when individuals with high exposure levels were examined and/or when increasing years of latency were assumed. For example, there

were five or fewer lung and colon–rectum cancer cases who were exposed to levels above the 90th percentile, and six or fewer cases who were exposed when 11 or more years of latency were considered. The length of time between PCE contamination and cancer diagnoses also precluded our ability to assume empirical latent periods greater than 15 years.

Furthermore, exposure misclassification was almost certain because the Webber–Brown model indirectly estimated the historical dose entering a household using limited information. Within each household, each resident's dose would be expected to vary with water consumption, type of use, and perhaps other characteristics such as household ventilation. Moreover, other sources of exposure may have been encountered outside of the home in the workplace, dining establishments, and other people's homes. On the other hand, stratifying the data by bottled water use and usual bathing habits improved the correspondence between the household exposure estimate and an individual's exposure. In addition, studies that have modeled exposure to volatile organic compounds have shown that inhalation exposure from bathing—a residential activity—often results in higher exposure than ingestion (18,19). In any event, because PCE exposure was assessed without knowledge of disease status, any errors would be unsystematic. Such errors likely bias the measure of association toward the null when the exposure is dichotomous (e.g., ever vs. never exposed), but they may bias the measure in either direction when exposure levels are examined (e.g., \leq median, $>$ median) (20).

Age at diagnosis or index year, vital status, sex, occupational use of solvents, occupational history associated with the cancer, and established cancer risk factors (such as cigarette smoking) were controlled in multivariate analyses, so the results are not plausibly explained by confounding. Residual confounding by other personal attributes or other exposures is improbable. To confound the observed associations, a hypothetical attribute would need to be strongly associated with the labyrinthine distribution of PCE exposure and a strong risk factor for the cancers under study—an unlikely combination of events. Furthermore, the public water supplies showed little contamination from other sources. No vinyl chloride and only low levels of benzene were detected. Trihalomethane levels were also low because only one of the eleven water supplies was chlorinated. The highest chloroform level detected in the sole chlorinated water supply was 13 ppb. No

associations were seen between lung and colon–rectum cancer and exposure to either the chlorinated surface water supply or the groundwater supply with evidence of solvent contamination (21).

Observation bias is also an implausible explanation of the findings. Although the interviewers knew the disease status of the subjects, they did not have any knowledge of the specific environmental exposures under investigation. PCE exposure was assessed independently of the interview, and assessors were unaware of the disease status of subjects. The use of deceased controls matched to deceased cases (and proxy interviews for both) also makes recall bias unlikely.

There was also no evidence of biased selection of cases or controls. Interview and follow-up rates were comparable for cases and controls, as were available demographic characteristics of participants and non-participants. Identification of cases was performed by the Massachusetts Cancer Registry, which has nearly complete reporting for the cancers under study (22).

Based on the available evidence from toxicologic and epidemiologic studies, the International Agency for Cancer Research currently considers PCE a “probable carcinogen” for humans (Group 2A) (23), while the United States Environmental Protection Agency considers it on a continuum between a “possible” and “probable” carcinogen (under current review) (24). Toxicologic studies have found hepatocellular carcinomas in mice following oral and respiratory exposure, and mononuclear cell leukemia and renal cancer in rats following oral exposure (23).

Most epidemiologic studies have been conducted among dry-cleaning workers, as PCE has been the major solvent used in this industry since the early 1960s. A Swedish case–control study reported a twofold increased OR for colon cancer among female dry cleaners (CI, 0.5–7.1) (25). In contrast, a National Cancer Institute (NCI) cohort study of 5,365 dry-cleaning workers found no increase for colon cancer (CI, 0.6–1.4) and a 40% elevated risk of rectal cancer (CI, 0.7–2.5) (26). A National Institute for Occupational Safety and Health (NIOSH) study of 1,701 dry-cleaning workers found a 56% increased risk of intestinal cancer (CI, 1.02–2.29) and a 27% increased risk of rectal cancer (CI, 0.41–2.97) (27). Results in a subcohort considered exposed only to PCE were null, but this group numbered only 620 and no latency or employment duration analyses were conducted.

A case–control study in Missouri found an 80% increased risk of lung cancer among nonsmoking Missouri women who were

ever employed in the dry-cleaning industry (CI, 1.1–3.0) (28). Those employed more than 13.5 months had a 2.9-fold increased risk of lung cancer (CI, 1.5–5.4). The NCI cohort study of dry-cleaning workers found a 30% excess of lung cancer deaths (CI, 0.9–1.7) (26), and the NIOSH study found a 19% increased risk of respiratory system cancers overall (CI, 0.87–1.59) and a 12% increased risk in the subcohort exposed only to PCE (CI, 0.61–1.88) (27). A causal interpretation of the NCI and NIOSH study findings is limited because neither study had information on cigarette smoking.

Other studies have measured the mortality experience of individuals in a broader category of employment—laundry and dry-cleaning work—which presumably is less closely correlated with PCE exposure (23,29–31). A study among female workers in Wisconsin found proportional mortality ratios (PMRs) of 103, 119, and 98 for colon, rectum, and lung cancer, respectively (29). A census study in Great Britain found a 3.3-fold increased risk of rectal cancer (CI, 0.7–9.7) among women, and a 70% increased risk (CI, 1.2–2.3) of cancer of the trachea, bronchus, and lung among men (23). A proportional mortality study of laundry and dry-cleaning workers in Oklahoma found a 70% increased risk of lung cancer (CI, 1.2–2.5) and decreased risks of colon and rectum cancer (standardized mortality ORs 0.6, and 0.9, respectively); however, PCE accounted for less than 50% of the dry-cleaning solvent used in Oklahoma during the study period (30).

The most recent study of cancer mortality experience among laundry and dry-cleaning workers found excesses for cancer of the trachea, bronchus, and lung among black and white men and women under the age of 65 (e.g., PMR 132, CI, 94–181 for black men) and among black women aged 65 years and older (PMR 128, CI, 94–170) (31). No or minimal excesses were observed for colon cancer. As in the NIOSH and NCI studies, the lung cancer excesses reported in the laundry and dry-cleaning worker studies are difficult to interpret because smoking data were not collected.

Thus, although these occupational studies were generally large and yielded fairly precise estimates of association, their validity was limited by the self-selected nature of the population, exposure measures based solely on job titles, reliance of mortality rather than incidence end points, and little information on confounding factors. In

contrast, our investigation of a residentially exposed population is smaller and less precise, but has greater validity. As described previously, selection and observation biases were improbable in our study. Furthermore, like the water distribution pattern seen in John Snow's investigation of the 1854 London cholera epidemic (32), PCE exposure in the Cape Cod area was distributed in a variety of neighborhoods and over many years, such that adjacent streets, and even adjacent houses, differed by amount of exposure. This unsystematic pattern of exposure, along with the low level of water contamination from other sources and the use of multivariate techniques to control for numerous other variables greatly reduced the likelihood of confounding.

In this light, we believe that the excesses of lung cancer and, to a lesser extent, colon-rectum cancer among individuals residentially exposed to high cumulative levels of PCE-contaminated drinking water should be taken seriously and followed up with a larger study. Given that PCE remains a commercially ubiquitous solvent and a common drinking water contaminant (24), its carcinogenicity has major ramifications for public health.

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