Drinking Water Mutagenicity and Gastrointestinal and Urinary Tract Cancers: An Ecological Study in Finland

ABSTRACT

Objectives. The purpose of this study was to investigate the relationship between exposure to mutagenic drinking water and cancers of the gastrointestinal and urinary tract.

Methods. Past exposure to drinking water mutagenicity was assessed in 56 Finnish municipalities for the years 1955 and 1970. The cases of bladder, kidney, stomach, colon, and rectum cancers were derived from two periods (1967 to 1976 and 1977 to 1986). Age, sex, social class, urban living, and time period were taken into account in the Poisson regression analysis.

Results. Statistically significant exposure-response association was observed between exposure and incidence of bladder, kidney, and stomach cancers. In an ordinary municipality using chlorinated surface water, this exposure would indicate a relative risk of 1.2 for bladder cancer and of 1.2 to 1.4 for kidney cancer compared with municipalities where nonmutagenic drinking water was consumed.

Conclusions. The acidic mutagenic compounds present in drinking water may play a role in the etiology of kidney and bladder cancers, but, because the results are based on aggregate data, they should be interpreted with caution. (*Am J Public Health.* 1994;84:1223–1228)

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Introduction

The carcinogenic and mutagenic compounds found in chlorinated drinking water have raised concern over the potential long-term health effects of water chlorination and chlorination by-products.[1–3] Epidemiological studies have suggested an association between chlorinated drinking water and cancers of the urinary and gastrointestinal tract, but the evidence of such a causal relationship has remained inconclusive.[4–6]

The production of chlorination by-products depends on raw water quality and chlorination practices. In epidemiological studies on water chlorination and cancer, the quantitative estimates of exposure are mainly based on the volatile fraction of organic material, which contains compounds such as trihalomethanes. Since most of the organic compounds in drinking water—including the mutagenic ones—are known to be nonvolatile[3] and also acidic,[7] the amount of trihalomethanes may not necessarily reflect the potential carcinogenicity of chlorination by-products found in drinking water.

So far, no epidemiological studies have been published on the association of exposure to mutagenic drinking water and the risk of cancer. Because of the high content of organic material—mainly humic substances—in raw waters, high levels of mutagenic activity have been observed in Finnish chlorinated drinking waters.[7] A major concern is 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), which has been shown to be a very potent bacterial mutagen[8] and genotoxic compound in laboratory animals.[9] The concentration of MX correlates well with the degree of mutagenicity.[10] MX has also been found in drinking waters in the United States,[11] Great Britain,[12] and Japan.[13] Thus, the purpose of this study was to investigate the relationship between exposure to mutagenic drinking water and risk of cancers of the gastrointestinal and urinary tract.

Subjects and Methods

It was important that the exposed and unexposed persons in the study be as comparable as possible with respect to other cancer risk factors. Thus, municipalities with large rural populations were excluded by limiting the study to those 63 Finnish municipalities administratively defined as cities or rural towns in 1950. To improve the validity of the study, municipalities with fewer than 2000 inhabitants, those with more than 80% of the population born outside the municipality, and those that had been merged with large rural municipalities were excluded from the study, thus reducing the number of municipalities to 56.

Numbers of new cancer cases were obtained from the population-based, na-

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TABLE 1—Number of Observed Cancer Cases and Age-Adjusted[15] (World Standard Population) Cancer Incidence per 1 Million Person-Years in the 56 Municipalities, by Sex and Time Period

	No. of Observed Cancer Cases				Cancer Incidence			
	Men		Women		Men		Women	
	1967–76	1977–86	1967–76	1977–86	1967–76	1977–86	1967–76	1977–86
Bladder	1147	1800	467	730	121	145	27	31
Kidney	883	1312	783	1167	91	110	49	56
Stomach	3110	2858	2877	2881	327	233	164	125
Colon	1058	1708	1760	2707	112	139	104	120
Rectum	939	1412	1251	1651	100	114	72	74

TABLE 2—Population Included in the Study, Percentage of Population within the Water Supply System, Average Drinking Water Mutagenicity,[a] Population Exposure,[b] and Range in Mutagenicity[a] in 1955, 1970, and 1985

	1955	1970	1985
Population, in millions	1.7	2.2	2.3
Population within water supply system, %	43	80	92
Average mutagenicity			
All municipalities	1300	1900	1300
All municipalities[c]	2200	2900	1200
Population exposure			
All municipalities	600	1500	1200
All municipalities[c]	1600	2600	1100
Range in mutagenicity	0–5700	0–6900	0–5400

[a]Net revertants per liter (net rev/L).
[b]Percentage of population within the water supply system multiplied by the mutagenicity level.
[c]Weighted by person-years from 1967 to 1986.

tionwide Finnish Cancer Registry. The multiple sources of information available guarantee an almost 100% coverage of all cancer cases in Finland.[14] The study focused on cancers of the stomach, colon, rectum, kidney, and bladder (*International Classification of Diseases,* 7th edition codes 151, 153, 154, 180, and 181, respectively). The observed number of cancer cases was obtained for each municipality by sex, age (5-year categories), and time period (1967 to 1976, 1977 to 1986). The expected number of cancer cases (5-year categories) was calculated for each stratum of sex, age, and period using the respective incidence rates for the total population of Finland. For the analysis, age was further pooled into four broad categories: 0 to 49, 50 to 64, 65 to 74, and from 75 years onward. In addition, age-adjusted incidence rates for all municipalities combined were calculated for both time periods (Table 1).

Assessment of Past Exposure to Mutagenic Drinking Water

The past exposure to drinking water mutagenicity was assessed with a method developed by Vartiainen et al.[16] for two time periods, using the index years 1955 and 1970 to adjust for time and exposure factors such as latency. Information on past routinely collected water quality parameters (e.g., permanganate consumption, pH, color, and ammonium and iron content), water treatment practices, and chemicals used (e.g., chlorine dose, pre- or postchlorination or both) in the municipal waterworks was collected from a questionnaire sent to the municipalities and from past surveys and archives of administrative authorities. The past drinking water mutagenicity was then assessed for both years on the basis of an equation[16] giving the estimated drinking water mutagenicity level in net revertants per liter (net rev/L). The drinking water mutagenicities for the equation were measured according to standard procedures[17] in the Ames test using *Salmonella typhimurium* bacterial tester strains TA100 and TA98 without enzymatic activation.

Water from different waterworks often gets mixed when used by consumers. In those municipalities with more than one waterworks, a mean was calculated weighted for the volumes of water supplied by the different waterworks. The exposure to drinking water mutagenicity was estimated to be zero for people living outside the public water supply system (private wells) as no mutagenicity has been observed in groundwaters.[16] For both years, 1955 and 1970, the population exposure (wm) was calculated by multiplying the proportion of the population within the municipal water supply system (w) by the estimated level of drinking water mutagenicity (m) (Table 2, Figure 1). For the statistical analysis, the level of mutagenicity was also categorized (no mutagenicity, less than 3000 net rev/L, and 3000+ net rev/L), and the average of mutagenicities in 1955 and 1970 was used. A more detailed evaluation and description of the past exposure assessment in terms of drinking water mutagenicity has been published elsewhere.[18]

Statistical Analysis

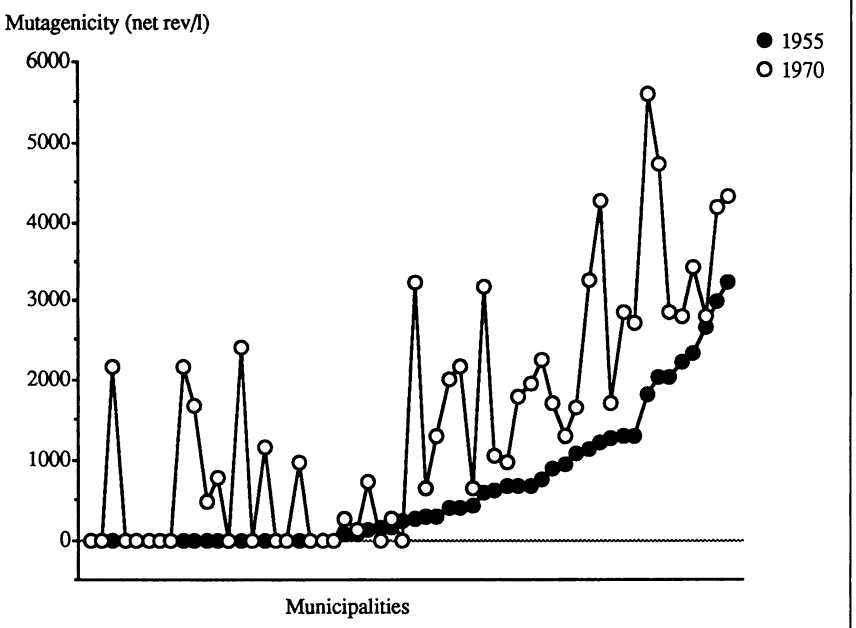
The observed numbers of cancer cases in each municipality were compared with the expected numbers of cancer cases based on the cancer incidence in the entire country in strata defined by sex, broad age group, and calendar period. The risk ratio (RR) between the observed and the corresponding expected number of cancer cases was modeled according to an additive relationship:

$$RR = \alpha + \gamma\, wm + \Sigma\theta_i\, s_i.$$

The baseline risk α was allowed to differ in strata defined by sex, age, calendar

period, and urban living. The parameter γ thus gives the change in risk ratio related to a unit of change in population exposure to mutagenicity (wm). In the control of confounding, the relative sizes of social classes in each municipality were used to describe life-style and smoking habits. The relative size of the two highest social classes out of four and the proportion of the lowest class in each municipality were derived from the 1970 census[19] and were used in the analysis as numerical variables (s_i, i = 1,2), with parameters θ_i specifying the relationship with social classes. The three largest cities in Finland, with their comparably more urban environments and life-styles, were grouped into a separate category in the analysis, and a categorical variable was created to adjust for a different base level of risk in these cities.

The statistical analysis was performed using GLIM[20] with an identity link function and a statistical model based on Poisson regression.[21] The effect of drinking water mutagenicity was studied as both a categorical and a numerical variable, and logarithmic transformations were also fitted. In the final analysis, the choice of the model with respect to mutagenicity was based on its ability to explain the variation in the data with fewest model parameters. This resulted in a linear model with a numerical variable for exposure to mutagenicity in the final analysis. Overdispersion was estimated to be of the order of 10%.[22] Adjusting for this would not have changed the confidence intervals (CIs) of the model parameters to any substantial extent. For purposes of illustration, the transformed coefficient, 1 + γ3000 net rev/L, was used to derive a risk ratio related to a typical mutagenicity exposure of 3000 net rev/L (Table 2). In further study of confounding, separate analyses were performed without the three largest cities, without eight municipalities that had 2% or more of the population working in the chemical industry,[23] and without six municipalities that had the highest levels of migration (an average annual in-migration of more than 8% from 1966 to 1970).[24] To focus the analysis on the exposure-response association and the quantity of the biologically active compounds in drinking water, the statistical analysis was also performed separately for those 34 municipalities in which the population was exposed to mutagenic drinking water. The proportions of cancer cases attributable to exposure were calculated[25] using the linear model and the average population exposure level of 1600 net rev/L in 1955 (Table 2).



Note. Exposures were estimated by multiplying the proportion of the population within the municipal water supply system by the mutagenicity level.

FIGURE 1—Estimated exposures to drinking water mutagenicity in the 56 municipalities in 1955 and 1970, arranged by the estimated exposures in 1955.

Results

Considering the population mutagenicity exposure as the only risk factor in the model, the risk ratios of cancers of the bladder, kidney, and colon were significantly higher than 1 (Table 3). In an average municipality with chlorinated surface water, the exposure to drinking water mutagenicity for those within the municipal water supply system was 2700 net rev/L in 1955 and 3300 net rev/L in 1970. Thus, in colon cancer, a risk ratio of 1.31 corresponded to an exposure of 3000 net rev/L, indicating a 10% unit increase for each addition of 1000 net rev/L, according to the linear exposure-response relationship used. After adjusting for the background variables (age, sex, time period, largest cities) and social class, the risk ratios diminished in kidney and colon cancers.

The risk of bladder cancer was 1.17-fold (95% CI = 1.03, 1.31) among exposed as compared with unexposed persons when adjusted for the potential confounders. The risk remained approximately the same when the analysis was restricted to the 34 municipalities with mutagenic drinking water. The adjusted risk ratio for kidney cancer was 1.08 (95% CI = 0.91, 1.24) in the total study population and 1.32 (95% CI = 1.11, 1.53) in the restricted analysis. The risk of stomach cancer was also slightly higher among the exposed, with an adjusted risk ratio of about 1.1. The adjusted risk of colon and rectum cancer among exposed persons did not differ from the corresponding risk for unexposed persons by more than could be expected by chance.

The exposure was assessed for 1955, and the cancer risk was calculated for 1967 to 1986 (Table 3). Taking into account cases diagnosed between 1977 and 1986 only, the adjusted risk ratios were approximately the same, with the exception of slightly higher risks in kidney cancer (RR = 1.16; 95% CI = 0.97, 1.36) (Table 4). Applying the average exposure from 1955 and 1970 and cases diagnosed between 1977 and 1986, the adjusted risk ratios for bladder cancer were lower than those given in Table 3 (RR = 1.05; 95% CI = 0.92, 1.19 for all municipalities). In contrast to bladder cancer, slightly higher risks were observed in stomach cancer (RR = 1.09; 95% CI = 1.02, 1.17 for all municipalities). The restricted analysis of

TABLE 3—Estimated Risk Ratio for a Typical Exposure to Chlorinated Surface Water (3000 net rev/L)

Site and Model[b]	All[a] Risk Ratio	All[a] 95% Confidence Interval	Mutagenic Water[a] Risk Ratio	Mutagenic Water[a] 95% Confidence Interval
Bladder cancer				
Mutagenicity	1.18	1.10, 1.27	1.21	1.10, 1.32
Plus age, sex, period, main cities	1.20	1.08, 1.33	1.24	1.09, 1.38
Plus social class	1.17	1.03, 1.31	1.21	1.02, 1.40
Kidney cancer				
Mutagenicity	1.37	1.27, 1.47	1.57	1.44, 1.69
Plus age, sex, period, main cities	1.23	1.10, 1.37	1.44	1.29, 1.60
Plus social class	1.08	0.91, 1.24	1.32	1.11, 1.53
Stomach cancer				
Mutagenicity	0.97	0.93, 1.01	0.99	0.93, 1.04
Plus age, sex, period, main cities	1.03	0.97, 1.09	1.06	0.99, 1.14
Plus social class	1.07	1.00, 1.13	1.11	1.02, 1.19
Colon cancer				
Mutagenicity	1.31	1.23, 1.39	1.39	1.30, 1.48
Plus age, sex, period, main cities	1.18	1.07, 1.27	1.25	1.13, 1.38
Plus social class	1.05	0.93, 1.17	1.09	0.93, 1.25
Rectal cancer				
Mutagenicity	1.05	0.97, 1.12	1.02	0.93, 1.12
Plus age, sex, period, main cities	1.02	0.92, 1.12	0.94	0.87, 1.12
Plus social class	1.05	0.93, 1.17	0.98	0.82, 1.14

[a]The risk ratios for cancer cases in 1967–1986 are calculated corresponding to exposure to drinking water mutagenicity in 1955 for all municipalities (n = 56) and municipalities with mutagenic drinking water (n = 34).
[b]Within each type of cancer, the variables listed are those added to the previous model.

municipalities with mutagenic drinking water resulted in slightly higher risk ratios for bladder, kidney, and stomach cancers. For other cancers, the change of time and exposure periods led to no major differences from the risk ratios reported above.

The analyses performed after exclusion of the three largest cities and the municipalities with the highest migration levels did not change the observed risk estimates. In kidney cancer, slightly higher risk ratios were observed after exclusion of the municipalities with chemical industry (Table 4). Interaction between exposure and gender was statistically significant ($P < .05$) only in kidney and colon cancers. For colon cancer, the adjusted risk ratios corresponding to those in Table 3 were 1.14 (95% CI = 0.92, 1.36) for men and 1.01 (95% CI = 0.87, 1.16) for women. The interaction between age and exposure was statistically significant ($P < .05$) in kidney cancer, with the greatest risk ratio observed among the oldest age group (Table 4).

The exposure-response association may be converted into the proportion of cancer cases from 1967 to 1986 attributable to drinking water mutagenicity. When the adjusted relative risks from the restricted analysis of municipalities with mutagenic drinking water in Table 3 are used, the calculated attributable proportions would be 10% in bladder, 15% in kidney, and 5% in stomach cancer. The respective numbers of new cancer cases between 1967 and 1986 may be derived by applying these proportions to the numbers of cases reported in Table 1.

Discussion

The results indicate that, in a typial municipality using chlorinated surface water (3000 net rev/L), the relative risks would be about 1.2 for bladder cancer, 1.2 to 1.4 for kidney cancer, and 1.1 to 1.2 for stomach cancer as compared with those persons not using mutagenic drinking water. When the exposed population is large, the detection and estimation of even small risks is important from the public health point of view. In the present study, the existence of a method for assessing the past exposure to drinking water mutagenicity, an accurate system of cancer registration, and a large variation in drinking water mutagenicities made it possible to demonstrate small, yet statistically significant excess cancer risks associated with the assessed past exposure to mutagenic drinking water.

The observation of an increased risk of bladder cancer is consistent with results of earlier case-control studies on drinking water chlorination and cancer.[4–6,26] An association between the exposure to chlorinated water and the occurrence of gastrointestinal cancers has also been reported in epidemiological studies.[4–6,27] Such an association was not observed in rectum and colon cancers in our study. In kidney and colon cancers, the observed difference in risk estimates by sex could be explained by higher consumption of water by men. Confounding by gender-related life-styles and occupations or interaction with other gender-related exposures and biological factors may also be involved. The observation of substantially higher relative risks for kidney cancer in the oldest age group is in line with a longer latency time. The observed increased risks of kidney and bladder cancers are in line with the pharmacokinetics of the strong water mutagen MX.[28] The protein-bound MX[29] may be released in the kidney and therefore may induce higher concentrations there than in most other tissues.[28] Although, according to current knowledge, MX is the compound of major concern, chlorinated compounds other than MX may also have a carcinogenic effect.

Socioeconomic status has been shown to be associated with the incidence of several cancers in Finland, including cancers of the colon, rectum, and kidney.[30,31] In the present study, social class was determined by occupation. In earlier studies, it has been shown to be associated with diet and way of life.[32] Occupation has been shown to be associated with smoking, explaining a large part of the variation in lung cancer incidence.[33] Therefore, social class may be regarded as a suitable surrogate variable for life-style, diet, and smoking on the population level. After the municipalities with the highest proportions of the population working in the chemical industry were excluded, the risk estimates were higher in bladder and kidney cancers. This finding may be owing to the confounding effect of chemical exposures in these municipalities. The population density is greater and the life-style different in the three largest cities. After social class variables were included in the model, the risk estimates were similar in the analyses with or without the three largest cities, which

TABLE 4—Risk Ratios for a Typical 3000 net rev/L Exposure in 1955 for Kidney Cancer When Background Factors and Social Class Are Included in the Model, Shown by Time Period and Chosen Restrictions

	Cancer Cases in 1967–1986				Cancer Cases in 1977–1986			
	All		Mutagenic Water		All		Mutagenic Water	
Restrictions	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
No exclusions	1.08	0.91, 1.24	1.32	1.11, 1.53	1.16	0.97, 1.36	1.44	1.18, 1.69
No chemical industry	1.17	1.01, 1.34	1.37	1.15, 1.59	1.26	1.06, 1.47	1.50	1.24, 1.76
Women	0.91	0.69, 1.13	1.21	0.93, 1.50	0.95	0.68, 1.22	1.28	0.94, 1.62
Men	1.26	1.02, 1.49	1.45	1.14, 1.75	1.39	1.10, 1.67	1.60	1.24, 1.97
Age group 75+	1.61	0.92, 2.30	2.46	1.62, 3.30	1.79	0.98, 2.61	2.52	1.50, 3.53

Note. RR = risk ratio, CI = confidence interval.

indicates that the confounding effect of urban living was taken into account. As the inclusion of social class in the multiple regression model may not fully adjust for life-style factors, the residual confounding from life-style factors such as smoking may not be totally excluded.

In a previous study of 86 drinking water samples, the correlation coefficient between the measured mutagenicity in TA100 Ames *S. typhimurium* tester strain and the modeled mutagenicity was 0.85.[16] Assessment of past exposure is based on historical observed raw water quality parameters and water treatment practices and therefore on the real historical situation, even though the actual historical mutagenicity may only be approximated. The methods for determining permanganate values of water samples have remained unchanged since the 1930s. In surface waterworks, the water quality data have been analyzed monthly; in ground waterworks they are analyzed usually once every four seasons. The approximation of historical mutagenicity was based on annual averages, derived from monthly measurements in surface waterworks. These values therefore represent potential seasonal variations.

The current understanding is that the mutagenic compounds in drinking waters are predominantly produced during water chlorination.[34] In an earlier survey, only one raw water source was shown to be mutagenic in the 1980s, and even in this case the mutagenicity of drinking water grew several times higher during water treatment.[16] Other exposures mediated by the water supply network, such as radioactive substances or asbestos from raw water or waterpipes, are unlikely,[35,36] and there is no evidence that these are related to drinking water mutagenicity. Until recently, consumption of bottled water and soft drinks has been very low in Finland, at least when compared with that in western and southern Europe and the United States.

The good coverage and quality of the Finnish Cancer Registry ensure the validity of the outcome assessment. Finland has a rather homogeneous population. During the 1960s, the direction of migration was from rural areas to towns, and therefore from areas of no or low exposure to high-exposure regions. In the 1970s and 1980s, migration between towns was also substantial. Confounding by migration would most probably diminish the estimated risks ratios.

Ecological studies are known to involve problems such as the ecological fallacy.[37] In the present study, the proportion of exposed persons was taken into account in each municipality, thus reducing the degree of ecological fallacy but not eliminating it, as the analysis was based on aggregate data. The fact that the expected rates were related to the whole country rather than to the chosen municipalities was taken into account by including in the model baseline risk parameters specific for sex, age, time period, and urban living. The Poisson distribution assumption of the number of observed cases enabled us to take into account the different sizes of the municipalities, and to study the proportion of persons exposed and the mutagenicity level of those exposed simultaneously in the analyses. The observed exposure-response association in the restricted analysis of municipalities with exposure to mutagenic drinking water indicated that the observed risk is more closely associated with the level of mutagenicity than with drinking water chlorination or mutagenicity as such.

Our findings suggest that the acidic mutagenic compounds present in chlorinated drinking water may play a role in the etiology of kidney, bladder, and possibly stomach cancer. Nevertheless, as the study was based on aggregate data, our results should be interpreted with caution. □

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