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Fluoride in Drinking Water and Cancer Mortality in Taiwan

Chun-Yuh Yang, Ming-Fen Cheng, Shang-Shyue Tsai, and Chung-Feng Hung

School of Public Health, Kaohsiung Medical College, Kaohsiung 80708, Taiwan

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The possibility that cancer risk is associated with naturally fluoridated water in Taiwan is examined. The 1982–1991 age-adjusted mortality rates for cancer for 10 municipalities whose water supplies contained the highest naturally occurring fluoride concentrations in Taiwan were compared to those rates for 10 matched municipalities with unfluoridated water. The two groups had similar urbanization levels and sociodemographic characteristics. Our study does not support the suggestion that fluoridation of water supplies is associated with an increase in cancer mortality in Taiwan. © 2000 Academic Press

Key Words: **fluoridation; drinking water; cancer; mortality; epidemiology.**

INTRODUCTION

The results of one study suggested that fluoridation of the drinking water in caused an increase in cancer mortality 10 United States cities compared with 10 other cities which did not have fluoridation of their drinking water (Yiamouyiannis and Burk, 1977). However, methodological weaknesses are evident in that study (Oldham and Newell, 1977). Data from the United States have been examined by several authors, who found that there was no evidence to suggest that increased cancer risk is associated with fluoridation (Hoover *et al*., 1976; Doll and Kinlen, 1977; Erickson, 1978; Rogot *et al*., 1978; Smith, 1980; Kinlen and Doll, 1981; Chilvers, 1982,1983). Studies in England and Wales (Cook-Mozaffari, 1981; Griffith, 1985) and in other localities (Goodall and Foster, 1980; Richards and Ford, 1979) also found no evidence that the addition of fluoride to water supplies increased the risk of dying from cancer.

These studies considered a wide range of populations and regions but were carried out mainly in the United States. The present study was done because few epidemiological studies have been conducted outside the United States (Cook-Mozaffari, 1981; Griffith, 1985; Goodall and Foster, 1980; Richards and Ford, 1979). There was a need for additional studies using new independent data from other populations; so we undertook the present study in Taiwan to explore further the association between cancer mortality and naturally fluoridated water supplies.

MATERIALS AND METHODS

Selection of Study Municipalities

Taiwan is divided into 361 administrative districts, which are referred to herein as municipalities. They are the units that were subjected to statistical analysis. Excluded from the analysis were 30 aboriginal townships and 9 islets, which have different lifestyles and living environments, and Taipei city (including 12 municipalities) and Kaohsiung city (including 11 municipalities), which have a distinctly more urban character and higher population than other Taiwan municipalities. Artificial fluoridation of municipal water supplies in Taiwan was introduced in only 1 municipality. This fluoridation program was then terminated in 1984 (Hsieh *et al*., 1986). The municipality which had artificial fluoridation was also eliminated from the analysis. This elimination of unsuitable municipalities left 299 municipalities for the analysis.

The measures of exposure to natural fluorides were obtained from the Taiwan Water Supply Corp. (TWSC) (TWSC/ROC, 1991), to whom each waterworks is required to submit drinking water quality data, including the levels of fluoride. The water samples were analyzed by the waterworks laboratory office using standard methods. For the analysis of fluoride, a SPADNS method was used (APHA, 1985). Since the laboratory office examines fluoride levels on a routine basis using standard methods, it was thought that the problem of analytical variability was minimal.

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Since the data on natural fluoridation were restricted to municipal water supplies, the study was restricted to those municipalities in which at least 75% of the municipality population was served by municipal water supplies. For the purpose of this study, two population groups were identified: one served by the naturally fluoridated water supplies (here designated "naturally fluoridated municipalities" (NFMs) and the other served by unfluoridated water supplies (here designated "unfluoridated municipalities") (UFMs). Those included in the NFMs were the 10 municipalities whose water supplies contained the highest concentrations of fluoride.

Mortality from cancer has been found to have regional variation in Taiwan (DOH/ROC, 1993), and several studies have examined the variation in cancer rates across urbanization gradients (Greenberg, 1983; Miller *et al.*, 1987; Swoboda and Friedal, 1991; Yang and Hsieh, 1998). To take into account the possible confounding effect resulting from differing urbanization levels, the urbanization level of the UFMs should be the same as that of the NFMs. The assignment of urbanization levels was based on the urban–rural classification of Tzeng and Wu (1986), which takes into account variables such as population density, age composition, mobility, economic activity and family income, educational level, and environmental- and health service-related facilities. This urbanization index was applied to the data of our previous studies (Yang *et al.*, 1996, 1997a). Each municipality in Taiwan ($n = 361$) was assigned to an urbanization category from 1 to 8. A municipality with the highest urbanization score, such as the Taipei metropolitan area, was classified in category 1, whereas mountainous areas with the lowest scores were assigned to category 8. The urbanization index used in this study serves as a proxy for a large number of explanatory variables, such as socioeconomic status and differential exposures to environmental conditions, which are related to the etiology of mortality.

More specifically, each NFM was matched with one UFM with the same urbanization level. If an NFM had more than one appropriate UFM for matching, a random sampling method was used to select one for matching.

Data Collection and Mortality Analysis

Information concerning both the number of deaths and the midyear population by sex, age, and calendar year during the years 1982–1991 was obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is in charge of the death registration system in Taiwan. The International Classification of Disease, Injury, and Causes of Death (9th revision [ICD-9]) is used to code the cause of death, and the system has been completely computerized since 1972.

Average annual cancer mortality rates per 100,000 population were calculated for males and females for each municipality in the two fluoridation groups for the period 1982–1991. As the age distribution was not similar among the municipalities of the two fluoridation groups, the age-standardized rates were computed using the direct method, using the world population in 1976 as the standard population (Waterhouse *et al.*, 1976).

Statistics

The age-standardized rates for various cancer sites were calculated first among residents in the individual naturally fluoridated and unfluoridated municipalities. The mean age-standardized rates in all NFMs and all UFMs were then calculated. The ratios of the mean age-standardized mortality rates from various malignant neoplasms for NFMs and the mean rates from all UFMs represent the relative cancer risk in the NFMs compared to that in the UFMs (standardized rate ratio, SRR). For the SRR the null hypothesis (H_0: SRR = 1) was tested, and the 95% confidence interval of the SRR was calculated according to the method of Rothman (1986).

RESULTS

The lowest fluoride concentration in drinking water in NFMs was 0.24 ppm. The sociodemographic characteristics of the NFMs and UFMs were generally similar, except for a higher population and population density among NFMs (Table 1).

Average annual age-adjusted cancer mortality rates per 100,000 population and ratios of the age-adjusted mortality rates (SRR) for 1982–1991 by cancer site and sex for the NFMs and UFMs are listed in Tables 2 and 3. Cancer rates for NFMs were generally similar to those for UFMs in both males and females, except for a significantly higher female bladder cancer mortality in NFMs.

DISCUSSION

Our study found an excess rate of bladder cancer that was restricted to females. It seems biologically implausible for fluoride to affect cancer rates for one sex only. Also, the NFMs and UFMs were reasonably

TABLE 1

Some Characteristics of Two Groups of Taiwanese Municipalities, Grouped According to Whether They Had Natural Fluoridation or Not

	10 NFMs[a]	10 UFMs[b]
Total population (1989)	673,806	500,467
Mean (median) population	67,380 (43,394) (20,549–182,352)[c]	50,047 (36,764) (24,381–147,508)[c]
Population density (per km^2)	1767.0	1465.0
Fluoride concentration (mg/L) mean (median)	0.24 (0.25) (0.24–0.28)[c]	< 0.01
Population served by municipal water supplies	90.3	91.8
White-collar, % [d]	30.2	29.6
Blue-collar, % [e]	25.8	26.6
Agriculture, % [f]	44.0	43.8

[a] Naturally fluoridated municipalities.
[b] Unfluoridated municipalities.
[c] Range (minimum, maximum).
[d] Professional, technical, administrative, superintendents, clerical, sales, and service workers as a percentage of total employed (aged 15 and over) population.
[e] Producers, transportation operators, and laborers as a percentage of total employed population.
[f] Farmers, loggers, grazers, fisherman, hunters, and related workers as a percentage of total employed population.

homogeneous in regard to several socioeconomic indicators, and there is no reason to expect sex differences in bladder cancer risk factors in the NFMs and the UFMs. Therefore, the possibility that this is a chance result should be considered because of the multiple comparisons carried out in this analysis. We, therefore, conclude that this study does not provide any evidence that fluoridation of the water supplies is associated with an increase in cancer mortality in Taiwan. Our finding agrees with past studies (Hoover *et al.*, 1976; Doll and Kinlen, 1977; Erickson, 1978; Rogot *et al.*, 1978; Smith, 1980; Kinlen and Doll, 1981; Chilvers, 1982,1983; Cook-Mozaffari, 1981; Griffith, 1985; Goodall and Foster, 1980; Richards and Ford, 1979).

TABLE 2

Mean Annual Age-Adjusted Mortality Rates per 100,000 Population and Ratios of Age-Adjusted Mortality Rates (SRR), 1982–1991, among Males in NFMs to Those in UFMs by Cancer Site

Cancer site (ICD 9)	10 NFMs	10 UFMs	SRR	(95% CI)[a]
All sites (140–208)	129.10	119.37	1.24	(0.96–1.22)
Esophagus (150)	5.22	4.66	1.12	(0.73–1.72)
Stomach (151)	13.42	13.05	1.03	(0.87–1.21)
Colon (153)	4.97	5.69	0.87	(0.55–1.39)
Rectum (154)	2.15	2.77	0.78	(0.48–1.24)
Liver (155)	34.88	32.35	1.08	(0.87–1.34)
Pancreas (157)	2.69	2.49	1.08	(0.73–1.58)
Lung (162)	26.46	25.23	1.05	(0.85–1.30)
Bone (170)	1.83	1.30	1.58	(0.92–2.17)
Prostate (185)	1.66	2.19	0.76	(0.42–1.36)
Bladder (188)	3.55	2.79	1.27	(0.75–2.15)
Kidney (189)	1.74	1.13	1.55	(0.84–2.84)
Brain (191)	1.15	0.79	1.45	(0.75–2.83)

[a] 95% confidence interval.

TABLE 3

Mean Annual Age-Adjusted Mortality Rates per 100,000 Population and Ratios of Age-Adjusted Mortality Rates (SRR), 1982–1991, among Females in NFMs to Those in UFMs by Cancer Site

Cancer site (ICD 9)	10 NFMs	10 UFMs	SRR	(95% CI)[a]
All sites (140–208)	76.09	66.36	1.15	(0.99–1.33)
Esophagus (150)	0.73	0.56	1.30	(0.41–4.10)
Stomach (151)	6.91	6.42	1.08	(0.80–1.44)
Colon (153)	5.93	4.10	1.45	(0.97–2.16)
Rectum (154)	1.84	2.61	0.70	(0.40–1.23)
Liver (155)	8.38	9.86	0.85	(0.67–1.08)
Pancreas (157)	1.90	1.67	1.14	(0.79–1.64)
lung (162)	10.22	9.78	1.05	(0.83–1.32)
Bone (170)	1.07	1.23	0.87	(0.52–1.44)
Breast (174)	4.88	4.22	1.16	(0.83–1.60)
Cervix uteri, uterus (179–180)	10.71	8.54	1.25	(0.98–1.60)
Ovary (183)	1.41	1.31	1.08	(0.68–1.70)
Bladder (188)	2.62	0.94	2.79	(1.41–5.55)[b]
Kidney (189)	1.13	0.82	1.37	(0.51–3.70)
Brain (191)	0.95	1.26	0.76	(0.44–1.30)

[a] 95% confidence interval.
[b] $P < 0.05$.

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations (Morgenstern, 1982). The completeness and accuracy of the death registration system should be evaluated before any conclusion based on the mortality analysis is made. In Taiwan, it is mandatory to register all deaths at local household registration offices and, since the household registration information is verified annually through a door-to-door survey, the death registration is very complete. Although causes of death may be misdiagnosed/or misclassified, the problem has been minimized through the improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, malignant neoplasms have been reported to be one of the most unequivocally classified causes of death in Taiwan (Chen and Wang, 1990). Because of their fatal outcome, it is believed that all cancer cases from the studied municipalities have had access to medical care, regardless of

geographical location, in recent years in Taiwan. The completeness and accuracy of death certificate registration is thus believed to be comparable.

Problems inherent in aggregate studies, including the "ecologic fallacy," are well known. However, the degree to which this fallacy is a problem varies from study to study. It was a distinct problem in the early water–cancer studies when associations between consumption of surface water and rates of cancer were investigated by comparing the proportion of county or parish residents supplied by surface water sources with cancer mortality rates for the total county or parish. In our study, the effects of fluoride in drinking water on cancer mortality were investigated using an "extreme points contrast" in order to maximize the inherent power of the design (Miettinen, 1985; Rothman, 1986). This method has been applied to our previous studies (Yang *et al.*, 1997b, 1998). We matched 10 municipalities with high levels of naturally occurring fluoride in their water supplies with control municipalities. Our previous study found a positive association between consumption of chlorinated drinking water and cancer of the rectum, lung, bladder, and kidney (Yang *et al.*, 1998). In this study, however, more than 90% of the NFMs and UFMs populations were served by municipal water supplies (In Taiwan, municipal water supplies are almost always treated with chlorine, the nonmunicipal sources are mainly privately owned wells (groundwater) and are often unchlorinated). Also, the municipalities selected for this study were rural municipalities and it is unlikely that much of the residents' budget was allocated to bottled water, thus reducing the likelihood of water coming from a source other than the home. In line with this assumption, we expect that persons, whether they live in NFMs or UFMs, do in fact drink water from the public supply or from private wells. Thus, the importance of one problem associated with ecologic analyses is reduced. We also believe that drinking chlorinated water was unlikely to have an effect on the present study because the percentages of the population served by chlorinated water in the NFMs and UFMs were similar (90.3% vs 91.8%).

Since the measure of effect in this study is mortality rather than incidence, migration during the interval between cancer diagnosis and death must also be considered. During this period, the cancer diagnosis may influence a decision to migrate and possibly introduce bias. If there are differences in migration patterns between the NFMs and UFMs due to proximity to medical care, for example, a spurious association between fluoridated water and cancer death would result. Since each NFM was matched with one UFM with the same urbanization level, this possibility should be minimized.

Smoking is an important risk factor for many of the cancers included. There is, unfortunately, no information available on the smoking patterns for individual study municipalities. Since the NFMs and UFMs were reasonably homogeneous for several socioeconomic indicators, we think that there is no reason to expect differences in smoking patterns between them.

In conclusion, our results do not support the suggestion that fluoridation of water supplies is associated with an increase in cancer mortality. However, even if fluoride increases cancer risk, such increases may not be observed in this study because the level of fluoride in the NFMs was quite low.

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