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Chlorination of Drinking Water and Cancer Mortality in Taiwan

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Chlorination has been the major strategy for disinfection of drinking water in Taiwan. An ecologic epidemiological study design was used to examine whether chlorination of drinking water was associated with cancer risks. A "chlorinating municipality" (CHM) was defined as one in which more than 90% of the municipality population was served by the chlorinated water while an "nonchlorinating municipality" (NCHM) was one in which less than 5% of the municipality population was served by chlorinated water. Age-adjusted mortality rates for cancer during 1982–1991 among the 14 CHMs were compared to rates among the 14 matched NCHMs with similar urbanization level and sociodemographic characteristics. The results of this study suggest a positive association between consumption of chlorinating drinking water and cancer of the rectum, lung, bladder, and kidney. Although these findings must be interpreted with caution because of limitations in the ecological study design, their public health significance should not be disregarded because chlorination of water is so widely practiced in Taiwan. © 1998 Academic Press

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

INTRODUCTION

The economy and effectiveness of chlorine in killing waterborne organisms has made water chlorination a tremendous public health success worldwide. Chlorination has been the major strategy for the disinfection of drinking water in Taiwan. It is currently added to approximately 75.8% of the nation's drinking water.

A number of epidemiologic studies have been conducted which examine the possible associations between consumption of chlorinated drinking water and cancer mortality or incidence (Page *et al*., 1976; Kuzma *et al*., 1977; Cantor *et al*., 1978,1987; Wilkins and Comstock, 1981; Young *et al*., 1981,1987; Bean *et al*., 1982; Gottlieb *et al*., 1982; Lawrence *et al*., 1984; Carpenter and Beresford, 1986; Cech *et al*., 1987; Zierler *et al*., 1988; Flaten, 1992; Morris *et al*., 1992; McGeehin *et al*., 1993). These studies consider a wide range of populations and regions but have been mainly carried out in the U.S. Most studies have shown positive associations between chlorinated drinking water and colorectal and bladder cancer. This has been attributed to trihalomethanes (THMs), a carcinogenic organic halogenated byproduct of water chlorination (Reuber, 1979; Dunnick and Melnick, 1993; IARC, 1987).

The present study was carried out because few epidemiological studies have been conducted outside the U.S. (Carpenter and Beresford, 1986; Flaten, 1992). The study reported here was designed to explore further the association between cancer mortality and the use of chlorinated water.

MATERIALS AND METHODS

Selection of Study Municipalities

Taiwan is divided into 361 administrative districts, which will be 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 had different lifestyles and living environments and Taipei city (including 12 municipalities) because of its distinctly more urban character and higher population than other Taiwan municipalities. This elimination of unsuitable municipalities left 310 municipalities for the analysis.

The current Taiwan water system is rather simple. Residents obtain their drinking water either from the public drinking water supply systems served by the Taiwan Water Supply Corporation (TWSC) or from nonmunicipal sources. The major sources of municipal water supplies are almost all

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surface waters and are often treated with chlorine. The nonmunicipal sources are mainly privately owned wells (groundwater) and are often unchlorinated.

In this study, an individual municipality was classified as a chlorinating municipality (CHM) if more than 90% of the municipality population was served by chlorinated water. In all, 156 of the 310 municipalities satisfied this criterion. A nonchlorinating municipality (NCHM) was defined as one in which less than 5% of the municipality population was served by chlorinated water, i.e., more than 95% of the residents of these 15 municipalities obtained their drinking water from unchlorinated water sources. In all, 15 municipalities satisfied this definition. These 15 NCHMs provide a unique opportunity to investigate the issue of chlorination.

Mortality from cancer has been found to vary between regions 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). To take into account the possible confounding effect resulting from differing urbanization levels, the urbanization level of the nonchlorinating municipalities should be the same as that of the chlorinating municipalities. The assignment of urbanization levels was based on the urban–rural classification of Tzeng and Wu (1986). This urbanization index has been applied to our previous studies (Yang *et al*., 1996,1997a). Each municipality in Taiwan ($n = 361$) was assigned to an urbanization category from 1 to 8. Municipalities with the highest urbanization score, such as the Taipei metropolitan area, were classified in category 1, while mountainous areas with the lowest score were assigned to category 8.

More specifically, each NCHM was matched with one CHM with the same urbanization level. Among the 15 NCHMs, one was excluded as there was no appropriate municipality for matching. If a NCHM had more than one appropriate CHM 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 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 revisions (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 of the two chlorination groups, 1982–1991. As the age distribution was not similar among the municipalities of the two chlorination groups, the age-standardized rates were computed by 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 chlorinating and nonchlorinating municipality. The mean age-standardized rates in all CHMs and all NCHMs were then calculated. The ratios of the mean age-standardized mortality rates from various malignant neoplasms for CHMs and the mean rates from all NCHMs represent the relative cancer risk in the CHMs compared to the NCHMs (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 sociodemographic characteristics of the CHMs and NCHMs were generally similar except for a higher population and a higher percentage of population using the chlorinated water among CHMs (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 CHMs and NCHMs are listed in Tables 2 and 3. A significant relationship was observed for cancers of the rectum, lung, bladder, and kidney in both males and females and for cancer of the liver in males. Mortality rates for cancers of the esophagus, stomach, colon, pancreas, prostate, brain, breast, cervix uteri and uterus, and ovary were not associated with the use of chlorinated water.

DISCUSSION

The major findings of this study suggest that there was a significant association between municipal (chlorinated) drinking water in Taiwan and mortality from certain cancers. Before evaluating the

TABLE 1

Some Characteristics of Two Groups of Taiwan Municipalities, Grouped According to Chlorination Practice

	14 CHMs[a]	14 NCHMs[b]
Total population (1989)	463,657	397,588
Mean population	28,399	33,118
Population density (per Km^2)	611.2	600.4
Percentage of population served by chlorinating water	96.1	1.5
White-collar, %[c]	25.4	24.8
Blue-collar, %[d]	24.6	22.2
Agriculture, %[e]	50.0	53.0

[a] Chlorinating municipalities.
[b] Nonchlorinating municipalities.
[c] Professional, technical, administrative, superintendents, clerical, sales, and service workers as a percentage of total employed (aged 15 and over) population.
[d] Producers, transportation operators, and laborers as a percentage of total employed population.
[e] Farmers, loggers, grazers, fishermen, hunters, and related workers as a percentage of total employed population.

meaning of these findings, consideration first must be given to the design of the study.

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations (Morgenstern, 1982). The completeness and accuracy of the death registration 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 this problem has been minimized through an 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 in recent years in Taiwan, all cancer cases from the studied municipalities have had access to medical care regardless of geographical location. 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 looked for 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 drinking water chlorination on cancer mortality were investigated using an "extreme points contrast" in order to maximize the inherent power of the design

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 Chlorinating Municipalities (CHMs) to Those in Nonchlorinating Municipalities (NCHMs) by Cancer Site

Cancer site (ICD 9)	14 CHMs	14 NCHMs	SRR (95% CI)[a]
All sites (140–208)	135.66	103.09	1.32 (1.18–1.46)[b]
Esophagus (150)	4.44	3.34	1.33 (0.83–2.12)
Stomach (151)	15.20	11.89	1.28 (0.98–1.67)
Colon (153)	5.00	4.65	1.08 (0.75–1.54)
Rectum (154)	3.45	2.43	1.42 (1.23–2.25)[b]
Liver (155)	36.45	29.37	1.24 (1.01–1.52)[b]
Pancreas (157)	2.81	1.88	1.49 (0.93–2.40)
Lung (162)	26.33	16.44	1.60 (1.39–1.85)[b]
Prostate (185)	2.14	1.81	1.18 (0.78–1.78)
Bladder (188)	4.85	2.60	1.86 (1.54–3.50)[b]
Kidney (189)	1.73	0.69	2.51 (1.27–4.94)[b]
Brain (191)	1.62	1.47	1.10 (0.58–2.09)

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

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 Chlorinating Municipalities (CHMs) to those in Nonchlorinating Municipalities (NCHMs) by Cancer Site

Cancer site (ICD 9)	14 CHMs	14 NCHMs	SRR (95% CI)[a]
All sites (140–208)	74.93	70.75	1.05 (0.95–1.18)
Esophagus (150)	0.52	0.81	0.64 (0.20–2.09)
Stomach (151)	7.16	5.85	1.22 (0.95–1.58)
Colon (153)	4.22	5.13	0.82 (0.59–1.14)
Rectum (154)	2.22	1.56	1.42 (1.13–1.98)[b]
Liver (155)	10.55	8.69	1.21 (0.90–1.64)
Pancreas (157)	1.87	1.53	1.22 (0.73–2.05)
Lung (162)	12.04	6.16	1.95 (1.45–2.59)[b]
Breast (174)	4.54	3.61	1.26 (0.89–1.77)
Cervix uteri, Uterus(179–180)	13.28	9.52	1.39 (0.88–1.86)
Ovary (183)	0.94	0.92	1.02 (0.47–2.23)
Bladder (188)	2.90	0.74	3.92 (1.08–4.28)[b]
Kidney (189)	1.54	0.70	2.20 (1.84–5.78)[b]
Brain (191)	1.25	1.57	0.80 (0.49–1.31)

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

(Miettinen, 1985; Rothman, 1986). This method was applied to our study of cancer mortality and residence near petrochemical industries (Yang *et al*., 1997b). The percentage of the population served by chlorinated water in the CHMs and NCHMs were 96.1 and 1.5%, respectively. Also, the municipalities selected for this study were rural municipalities and it is likely to preclude much of the resident's budget being 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 living in the CHMs do in fact drink water from the public supply and residents living in NCHMs do in fact drink water from the private wells (nonchlorinated water). Thus, the importance of one problem associated with ecologic analyses is reduced.

Migration is especially important in cancer studies, since the latency period is probably very long. The migration that does occur will result in a reduction of the strength of the geographical association between the disease and the studied factor (Polissar, 1980; Bentham, 1988). Taiwan's population is rather stationary compared with those of most other Western countries. It was reported that more than 90% of rural residents lived in the same municipality in which they were born for their entire life (Wu *et al*., 1989). Thus, the migration problem is probably minor.

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 is a different trend toward migration between the CHMs and NCHMs due to proximity to medical care, for example, a spurious association between chlorinated water and cancer death would result. Since each NCHM was matched with one CHM with the same urbanization level, this possibility should be minimized.

Potential exposure to industrial pollution for the population not necessarily working in the cancer risk industrial plants but living nearby may be another confounding factor. In this study, we used the percentage of a municipality's total population employed in the chemical and petrochemical industries as an indicator of a resident's exposure to air emissions from industrial plants (Yang *et al*., 1997b). The workers employed in chemical and petrochemical industrial plants constituted only 0.36% of the CHMs' population, while for the NCHMs this value was 0.39% (MOE/ROC, 1989). This result suggests that industrial pollution was unlikely to have an effect on cancer mortality.

The bladder and the rectum both serve a similar physiological function, storing concentrated excretory products. One might speculate that the epithelial tissue at both sites is exposed to high levels of chlorination by-products and is therefore at increased risk for the development of neoplasia. Our study is in accordance with many past studies (Page *et al*., 1976; Cantor *et al*., 1978, 1987; Kuzma *et al*., 1977; Moriris *et al*., 1992; Flaten, 1992; McGeehin *et al*., 1993). The lung is a biologically plausible target organ, since it is a major excretory route of ingested chloroform (Fry *et al*., 1972) and a site of considerable enzymatic metabolism of toxic compounds (Becker, 1975). Our finding is consistent with previous studies (Cantor *et al*., 1978; Jolley *et al*., 1978). Kidney and liver have been suggested as target organs on the basis of experimental animal study (Reuber, 1979), and cancer of these organs has been reported to be associated with the use of chlorinated water (Wilkins *et al*., 1979). The same holds for cancer of the kidney in both males and females in Taiwan and cancer of the liver for males. It seems biologically implausible for chlorinated by-products like trihalomethanes to affect cancer risk for one sex only. Also, a sex-specific effect in this direction is not consistent with the hypothesis that women may be more routinely exposed to domestic water sources than men. Alcohol drinking has been found to be associated with liver cancer (Yu *et al*., 1983; Oshima *et al*., 1984; Tsukuma *et al*., 1990; Chen *et al*., 1991). There is unfortunately no information available on alcohol consumption patterns for individual municipalities. If alcohol drinking were more prominent in the CHMs, one would expect liver cancer excesses in both male and female residents. Our results, however, indicate that excess liver cancers were restricted to men. Since the CHMs and NCHMs were reasonably homogeneous for several socioeconomic indicators, there is no reason to expect sex differences in alcohol drinking between the CHMs and the NCHMs. Therefore, the possibility that this is a chance finding should be considered.

The associations between exposure to chlorinated water and mortality from rectum, lung, bladder, and kidney cancer for both sexes were significant in this study. These results were not readily explained by confounding due to degree of urbanization, sociodemographic characteristics, or industrial pollution. The most important potential confounders not adjusted for in this study are diet and smoking. If consumption of a diet high in fat and low in fiber or smoking rates were associated with consumption of chlorinated water, one could argue that the observed association is confounded by dietary factors or

smoking. There is unfortunately no information available on the smoking and dietary patterns for individual study municipalities. Since the CHMs and NCHMs were reasonably homogeneous for several socioeconomic indicators, this possibility would have tended to be diminished. In addition, if diet were responsible for the observed association with rectal cancer, we would expect to see the same association with colon cancer (Morris *et al*., 1992). Also, there is no reason to expect differences in smoking patterns between CHMs and NCHMs in the present study. Therefore, the marked differences in these associations tend to refute the contention that smoking and diet are explanatory factors for observed associations.

In conclusion, the results give some support to indications from other epidemiological studies that chlorination of drinking water may be associated with cancer of the rectum, lung, bladder, and kidney. Due to inherent methodological limitations in ecological studies like the present one, the results could not provide sufficient evidence to establish a causal relationship. However, the public health significance of a cancer risk associated with consumption of chlorinated drinking water may be substantial. Our findings are in no way intended to suggest that the disinfection of drinking water with chlorine should be abandoned. However, it should not be forgotten that the primary public health concern for drinking water supplies is still waterborne infectious disease transmission, against which chlorine provides very effective protection. Therefore, these findings should provide an impetus to identify, develop, and implement disinfection strategies that are not associated with adverse health effects.

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