ORIGINAL CONTRIBUTION

Relationship Between Fluoride Concentration in Drinking Water and Mortality Rate from Uterine Cancer in Okinawa Prefecture, Japan

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The Okinawa Islands located in the southern-most part of Japan were under U.S.administration from 1945 to 1972. During that time, fluoride was added to the drinking water supplies in most regions. The relationship between fluoride concentration in drinking water and uterine cancer mortality rate was studied in 20 municipalities of Okinawa and the data were analyzed using correlation and multivariate statistics. The main findings were as follows.

(1) A significant positive correlation was found between fluoride concentration in drinking water and uterine cancer mortality in 20 municipalities ($r=0.626$, $p<0.005$).
(2) Even after adjusting for the potential confounding variables, such as tap water diffusion rate, primary industry population ratio, income gap, stillbirth rate, divorce rate, this association was considerably significant.
(3) Furthermore, the time trends in the uterine cancer mortality rate appear to be related to changes in water fluoridation practices. *J Epidemiol*, 1996 ; 6 : 184-191.

correlation analysis, fluoride, multivariate analysis, time trends, uterine cancer

Water is an essential component of the human body. Even small fluctuations can influence health. Kobayashi [1] first reported a relationship between the concentration of chemical components (SO_4 / $CaCO_3$) in river water and the mortality rate from cerebrovascular disturbances. Since then, the association between inorganic components of drinking water and the mortality rate from various diseases has been reported by other researchers around the world[2-14].

Recently, several studies have reported a relationship between the quality of untreated water and the mortality rate from cancer [15] and between trihalomethane and cancer of the urinary organs[16,17].

Okinawa prefecture is made up of approximately 150 islands that range over 400 km from south to north and 1,000 km from east to west, and are centered at 26° N.L. and 127° E.L. (Figure 1). Okinawa is subtropical, oceanic and insular, and therefore its natural evironment differs considerably from mainland Japan. Within Okinawa prefecture itself, environmental conditions such as weather, dietary habits and way of life do not differ considerably. However, other factors such as geological features, soil, population density, degree of development, area ratio of military bases show regional differences. Regional characteristics are also seen in the quality of drinking water supplied to the municipalities.

Administrative power of Okinawa was returned in 1972 from the U.S. to Japan. However, the water treatment methods developed during the U.S. administration which included the addition of sodium fluoride and sodium metaphosphate to tap water were continued. Thus, studying the ecologic epidemiological influence of the drinking water quality on the health of Okinawan people is considered highly relevant.

The present author has previously reported a correlation between the concentration of 15 components in drinking water and the mortality rate from various diseases (14 in female, 12 in male, 12 in both sexes) in Okinawa prefecture and a statistically signifiant correlation been observed between fluoride and

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uterine cancer as well as between ABS and ischemic heart disease, NO_3 levels and liver cancer [18]. The present paper explores epidemiologically the association between fluoride level and uterine cancer mortality using correlation and multivariate analyses. Uterine cancer here includes both cancer of the corpus and the cervix.

Although fluoride treatment of community water has been surrounded by controversy regarding the possibility of adverse health effect, the carcinogenicity of fluoride remains unclear [19].

MATERIALS AND METHODS

Municipalities Investigated

Twenty of the 53 municipalities in Okinawa prefecture, Naha City, Okinawa City, Ginowan City, Urasoe City, Itoman City, Gushikawa City, Ishikawa City, Nago City, Kin Town, Kadena Town, Chatan Town, Nishihara Town, Yonabaru Town, Sashiki Town, Haebaru Town, Kochinda Town, Motobu Town, Katsuren Town (the above being in the Okinawa Island proper), Hirara City (Miyako Island), Ishigaki City (Ishigaki Island) were investigated. Thirty-three municipal villages were excluded from the analysis, because their population scales (mean population: 6,882 in 1985) [20] were very small and their socioeconomic-medicare levels (mean income gap: 34.6 in 1985 and mean number of doctors: 1.5 in 1980) [20, 21] were considerably lower than those of the cities and towns (mean population: 47,599 in 1985; mean income gap: 52.4 in 1985; mean number of doctors: 37.3 in 1980) [20, 21].

Drinking Water Quality

Long-term drinking water quality data collected from 1968 to 1980 (Tohyama unpublished data) were analyzed. Trihalomethane content was analyzed over three years (1978,1979,1980). Analyses were conducted in accordance with the Standard Method for the Examination of Water and Wastewater [22], and fluoride was determined by the alizarine complexon method.

Mortality Rate

To establish the mortality rate, the number of deaths due to a specific cause for fiscal 1980 according to the Statistics / Information Department, Secretariat of the Ministry of Health

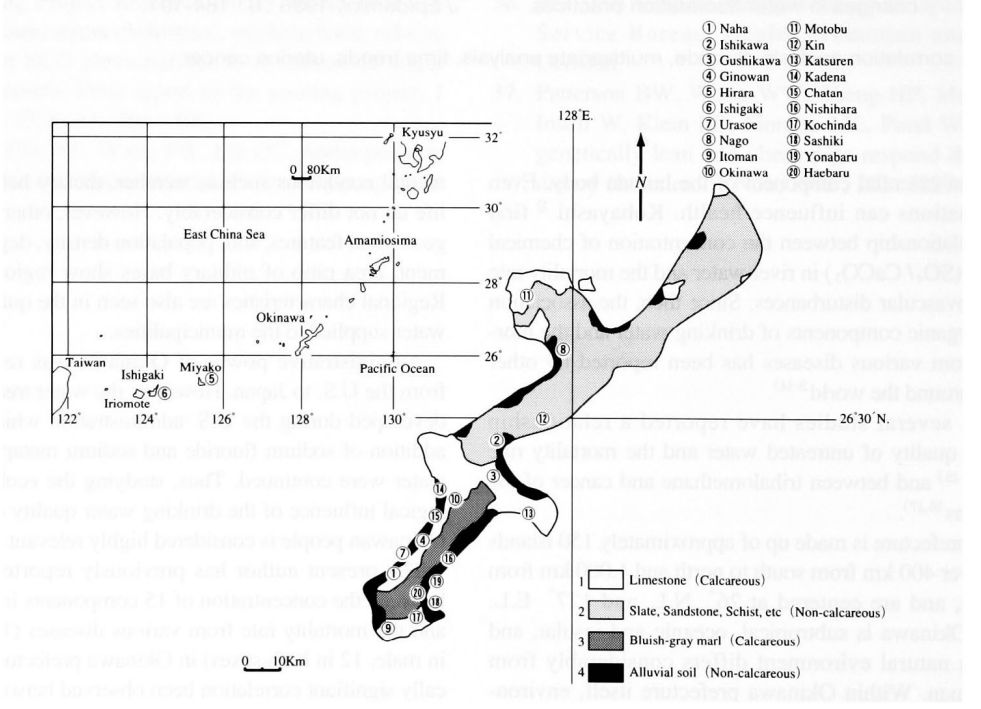

Figure 1. Location of Okinawa prefecture and its geological features.
(Drinking water type:
Calcareous-Itoman, Kochinda, Urasoe, Chatan, Ginowan, Okinawa, Kadea, Gushikawa, Katsuren, Hirara
Non-calcareous-Sashiki, Naha, Haebaru, Yonabaru, Nishihara, Ishikawa, Motobu, Nago, Ishigaki)

and Welfare, Japan[23] was used. The population according to sex from the national census taken in 1980 was used to determine the national population. The number of deaths according to municipality in Okinawa prefecture was calculated by averaging the values for 13 years from 1973 to 1985 in the mortality statistics caluculated by the Ministry of Health and Welfare. The population according to age of municipalities over a 5-year period was computed by averaging the numbers for 13 years that correspond to the number of deaths using the Okinawa prefecture's Statistical Yearbook[21]. The 5-year mortality rate between 1973 to 1992 was determined in order to study the time trend using the same method described above. S M R[24] by cause of death for each municipality in Okinawa was used for consultation.

Socioeconomic and Uterine Variables

The population density, the primary and secondary industry-population ratios and the income gap in 1985 (with the national average of Japan considered as 100%) for the 20 municipalities of Okinawa prefecture were obtained from the Minryoku[20]. The tap water diffusion rate in 1975 and percapita water consumption per day were obtained from the Outline of Tap Water in Okinawa Prefecture[21], and stillbirth, marriage and divorce rates were found in the Okinawa prefecture statistical yearbook (1980)[21]. The differences of two above mentioned values between 1975 and 1985 for the individual municipalities are well below 10% the sums of the same two values.

Analysis

PC-SAS (Statistical Analysis System)[26,27] was used for basic statistical analysis. Personal Computer Statistical Analysis Handbook II, Multivariate Analysis[28] was used for multiple regression analysis using a backward elimination procedure in order to screen variables for inclusion in the final model.

RESULTS

Drinking water quality

The concentrations of 15 components in drinking water from 1968 to 1980 in the 20 municipalities were averaged in order to investigate the overall water quality in Okinawa prefecture. The results are shown in Table 1. As shown in Table 1, dissolved solids range from 106.17mg/*l* to 485.49mg/*l*, and the range is wide. Also, fluorides are scattered with a minimum 0.02mg/*l* and maximum 0.37 mg/*l*. These concentrations can be divided into two groups, namely one greater than 0.19mg/*l* and the other less than 0.03mg/*l*.

Relationship Between Fluoride Concentration and Uterine Cancer Mortality Rate

Pearson's correlation analysis was used to evaluate the relationship between fluoride concentration in drinking water and

Table 1. Mean drinking water quality (mg /*l*) of 20 municipalities in Okinawa, Japan (1968～1980)

	NO_3	Cl	COD	F	Hard	ABS	THM	Ca	Mg	Na	K	SO_4	HCO_3	SiO_2	PO_4	D. Solids
①	1.08	36.4	3.00	0.34	129.4	0.14	0.04	43.9	4.2	29.8	2.5	22.1	136.8	12.6	0.18	290.08
②	0.29	31.9	2.76	0.27	71.3	0.00	0.04	22.3	3.8	29.0	2.8	14.0	73.3	13.8	0.02	191.52
③	3.71	48.4	2.72	0.34	244.6	0.17	0.05	88.9	6.1	31.2	2.0	28.3	248.2	10.0	0.25	467.62
④	2.61	46.3	3.21	0.37	235.8	0.44	0.04	86.1	5.1	31.9	2.1	30.8	253.6	10.4	0.44	470.20
⑤	5.95	42.5	1.65	0.02	217.5	0.00	0.01	79.1	4.7	28.0	1.8	20.8	227.3	5.7	0.08	415.96
⑥	0.25	26.9	2.64	0.02	24.3	0.02	0.03	5.3	2.6	16.3	1.1	8.9	26.6	18.1	0.05	106.17
⑦	2.50	44.4	2.92	0.27	216.6	0.26	0.04	78.3	5.0	31.2	2.0	25.1	232.7	10.6	0.39	432.76
⑧	1.47	63.3	2.07	0.02	153.4	0.05	0.03	47.2	8.1	38.2	3.3	16.1	160.8	15.5	0.08	353.45
⑨	5.32	34.7	1.92	0.19	202.5	0.10	0.04	66.2	8.5	28.5	1.9	22.9	245.3	10.2	0.30	424.15
⑩	2.97	45.9	3.32	0.32	234.8	0.41	0.05	85.3	5.2	31.7	2.1	30.6	252.8	10.5	0.47	468.32
⑪	1.46	25.2	1.24	0.03	158.1	0.06	0.01	51.2	6.9	18.4	1.5	14.9	168.3	12.1	0.10	300.16
⑫	4.14	35.6	2.08	0.32	238.0	0.03	0.04	78.1	9.8	31.3	2.0	21.8	291.7	10.4	0.26	485.49
⑬	3.56	48.6	2.73	0.37	227.2	0.17	0.05	81.6	5.6	31.5	1.7	23.9	242.9	10.2	0.27	450.42
⑭	2.91	46.1	2.97	0.33	237.1	0.40	0.05	85.9	5.1	32.9	2.1	30.5	257.3	10.5	0.48	474.57
⑮	2.96	46.3	2.98	0.34	237.1	0.41	0.05	86.6	5.2	32.8	2.1	30.4	258.0	10.6	0.48	476.23
⑯	0.14	28.2	2.19	0.32	53.2	0.01	0.04	16.0	3.4	21.6	1.1	15.9	55.5	12.6	0.03	154.84
⑰	6.64	34.5	0.95	0.03	223.7	0.08	0.01	78.1	5.3	28.5	1.5	22.7	212.8	6.3	0.09	396.55
⑱	0.40	34.3	2.69	0.33	74.2	0.02	0.04	23.3	3.9	30.5	3.1	17.8	76.6	14.0	0.03	204.32
⑲	0.38	34.2	2.68	0.31	74.0	0.06	0.04	23.2	4.0	30.5	3.1	18.0	76.5	13.9	0.05	204.24
⑳	0.44	32.7	2.51	0.31	75.7	0.10	0.04	24.1	3.8	27.3	2.4	18.4	79.7	13.9	0.10	203.29

① Naha	⑥ Ishigaki	⑪ Motobu	⑯ Nishihara
② Ishikawa	⑦ Urasoe	⑫ Kin	⑰ Kochinda
③ Gushikawa	⑧ Nago	⑬ Katsuren	⑱ Sashiki
④ Ginowan	⑨ Itoman	⑭ Kadena	⑲ Yonabaru
⑤ Hirara	⑩ Okinawa	⑮ Chatan	⑳ Haebaru

uterine cancer mortality rate in the 20 municipalities of Okinawa prefecture. The results showed a correlation coefficient of r=0.626 ($p<0.005$). A scatter graph of these data is shown in Figure 2.

Multiple Regression Analysis of Uterine Cancer Versus Fluoride and Socioeconomic-Uterine Variables

Water quality and other socioeconomic-uterine variables that are considered to be related to uterine cancer mortality rate are listed as potential risk factors in Table 2. Using the uterine cancer mortality rate (1973-1985)in the 20 municipalities shown in Figure 2 as the criterion variable, and using fluoride concentration (1968-1980), tap water diffusion rate (1975), percapita water consumption per day (1975), population density (1985), primary and secondary industry population ratios (1985), income gap (1985), stillbirth rate (1980), marriage rate (1980) and divorce rate (1980) shown in Table 2 as the explanatory variables, multiple correlation analysis by the variable selection procedure was carried out. The results are listed in Table 3. The explanatory variables selected in the final model were fluoride concentration, income gap, stillbirth rate, tap water diffusion rate and divorce rate. The highest significance was that of fluoride concentration.

Time Trend

The time trends of water fluoridation were studied by analyzing the changes in fluoride concentration over time in several municipalities. The results are shown in Figure 3 and 4. The 5-year uterine cancer mortality rates in either fluoridated or non-fluoridated municipalities were also compared over 4 consecutive time periods (1973-'77, 1978-'82, 1983-'87, 1988-'92). The results are shown in Figure 5 As shown in Figure 3, the fluoride level declined suddenly in 1972 when sodium fluoride addition was discontinued. The fluoride level in Figure 4 is very low and does not change substantially. When the two curves in Figure 5 are compared, the slope of curve A-fluoridated (15 municipalities) appears to be sharper than that of curve B-non-fluoridated (5 municipa lities). The mortality shown by curve A is higher for every time period compared to that of curve B. However, in the last period (1988-'92), the mortality shown by curve A approaches that of curve B.

DISCUSSION

Surface water is the primary source of drinking water in Okinawa prefecture.Compared to the average qualitiy of river water in the rest of the world, Ca, HCO_3[29] levels are higher outside of Japan because of the high lime stone content, whereas SiO_2[30] is higher in Japan due to the influence of volcanic geology and soil, and Cl, Na, SO_4[31] levels are higher in Okinawa due to direct influence of sea water on the small islands. The mean concentration of dissolved solids is 119.8 mg/*l* in the rest of the world, 86.4 mg/*l* in Japan, and 253.4 mg/*l* in Okinawa. When Okinawa is divided roughly into two regions, the non-calcareous area and the calcareous area, the dissolved solid content is markedly higher in the latter region, 592.2 mg/*l* compared to 111.2 mg/*l* [32].The drinking water quality in the 20 municipalities in Okinawa prefecture reflects the same characteristics as those of the water sources. Judging together from Table 1, Figure 1, Figure 3 and Figure 4, fluoride concentrations less than 0.03mg/*l* are attributed to natural origins and do not seem to be subject to the infuences of other water contents and the local calcareous or non-calcareous geology.However, concentrations greater than 0.19mg/*l* occur as a result of fluoridation of municipal water supplies. Fluoride supplementation was added to tap water in municipalities such

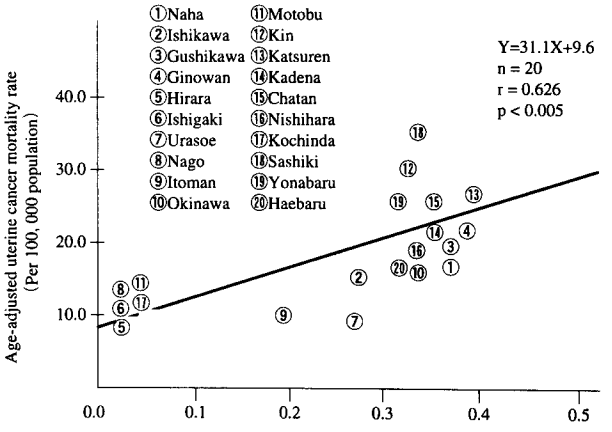

Figure 2. Scatter plot of fluride concerntration versus uterine cancer mortality rate.

Table 2. Independent variables used in multiple linear regression analysis of uterine cancer rates of 20 municipalities in Okinawa, Japan.

Variable	Mean	Standard Deviation	Range
F*concentration (mg / l)	0.24	0.14	0.02 ~ 0.37
Tap water diffusion rate (%)	85.9	18.7	44.4 ~ 100.0
Percapita water consumption (l / day)	325.5	86.6	145.0 ~ 491.0
Population density (/ km^2)	1721	1908	181.0 ~ 7970
Population in primary industry (%)	11.8	8.4	1.0 ~ 30.0
Population in secondary industry (%)	22.8	3.8	16.0 ~ 34.0
Percapita income gap (%)	52.4	10.3	31.7 ~ 70.9
Stillbirth rate (/ 1000 births)	23.9	9.2	6.1 ~ 48.9
Marriage rate (/ 1000 population)	7.5	0.77	6.3 ~ 8.9
Divorce rate (/ 1000 population)	1.7	0.56	0.84 ~ 2.91

* F : fluoride

Table 3. Results of multiple regression analysis of uterine cancer mortality versus variables listed in Table 2 for 20 municipalities in Okinawa, Japan.

	Regression coefficients and intercept		
Variables selected in final model	Estimate	Standard error	Significance
F*concentration (mg / l)	37.00	7.96	p<0.001
Income gap (%)	-0.28	0.13	p<0.058
Stillbirth rate (/ 1000 births)	-0.21	0.12	p>0.119
Tap water diffusion rate (%)	0.12	0.07	p>0.121
Divorce rate (/ 1000 population)	-3.29	2.25	p>0.166
Intercept	22.93	6.17	p>0.003

* F : fluoride

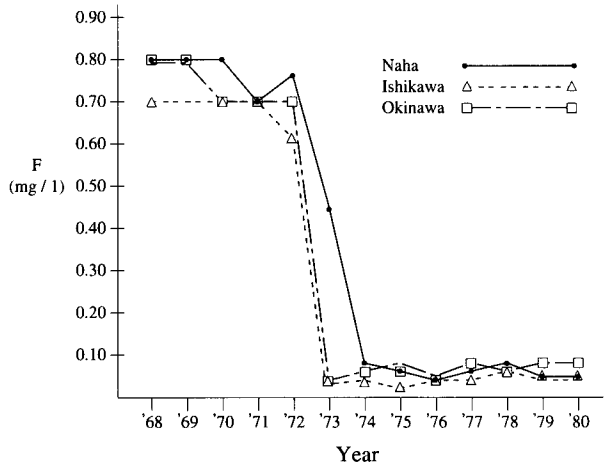

Figure 3. Secular changes in fluoride concentration of drinking water for 3 typical fluoridated municipalities.

as Naha City, Ishikawa City, Gushikawa City, Ginowan City, Urasoe City, Itoman City, Okinawa City, Kin Town, Kadena Town, Chatan Town, Nishihara Town, Sashiki Town, Yonabaru Town and Haebaru Town during the 27-year U. S. administration of Okinawa prefecture from 1945 to 1972, whereas municipalities such as Nago City, Motobu Town, Kochinda Town, Hirara City and Ishigaki City received no fluoride supplementation. The mean fluoride concentration over the 13 years in the municipalities supplemented with fluoride was between 0.19 and 0.37 mg/*l*, whereas that in municipalities which recieved no fluoridation was between 0.02 and 0.03 mg/*l*.

As can be seen in Figure 2, the uterine cancer mortality rate shows a significantly positive correlation with the fluoride concentration in drinking water ($r=0.626$, $p<0.005$). Using the regression line in Figure 2, the uterine cancer mortality rate in the municipalities supplemented with fluoride at a concentration of 0.30 mg/*l* (mean over 13 years) is 69.5% higher than that in the municipalities at zero fluoridation.

Weak associations in epidemiological studies are always sensitive to the influence of confounding variables. In Table 2, the tap water diffusion rate, percapita water consumption, population density, population in primary and secondary industies and stillbirth rate, marriage rate, divorce rate are considered to be confounding variables. The first 5 variables are considered to be socioeconomic factors and the latter 3 uterine factors.

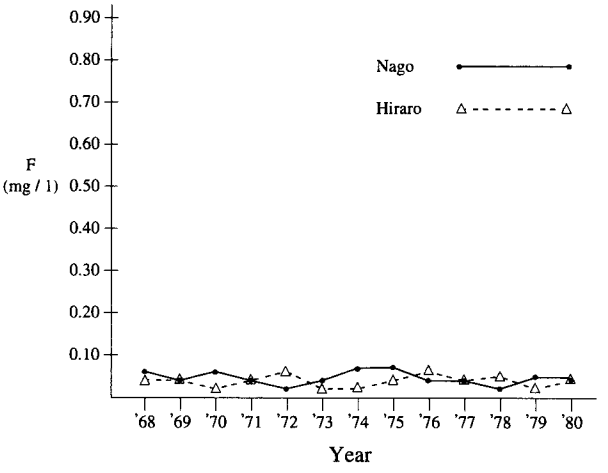

Figure 4. Secular changes in fluoride concentration of drinking water in 2 typical non-fluoridated municipalities.

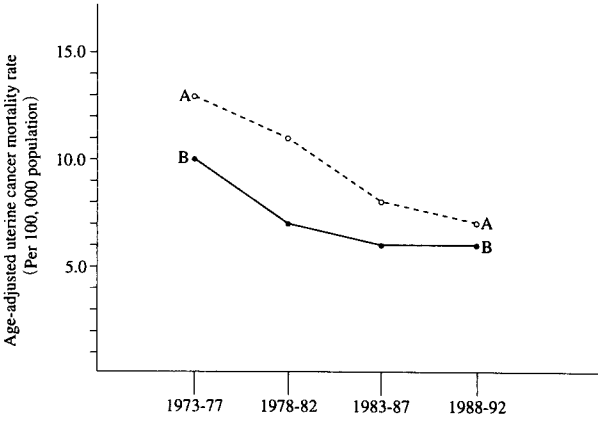

Figure 5. Uterine cancer mortality rate over a 5-year time period (1973-1992) for fluoridated municipalities (A, open circles) and non-fluoridated municipalities (B, filled circles).

The significance levels of the fluoride concentration, income gap, stillbirth rate, tap water diffusion rate and divorce rate, which were selected for the final model of the multiple regression analysis (Table 3), were $p<0.001$, $p<0.058$, $p>0.119$, $p>0.121$ and $p>0.166$, respectively. Of these variables, the significance of fluoride concentration was considerably higher. In other words, the relationship between fluoride level and uterine cancer mortality rate appears to be considerably stronger even after controlling for the effects of other confounding factors.

As shown in Figure 3, the fluoride concentration decreased sharply in 1972 from the previous level of 0.70~0.80 mg/*l* to the natural concentration (0.02~0.03 mg/*l*) shown in Figure 4. The mortality rate for both types of water treatment decreased over time from 1973 to 1992 in Figure 5. However, the slope of curve A- fluoridated was steep. Therefore, uterine cancer mortality rate in fluoridated municipalities appears to have declined rapidly subsequent to cessation of fluoridation. Thus, the time trends between fluoride concentration in drinking water and uterine cancer mortality rate appear to be nearly identical in the two geographical divisions.

According to the age-adjusted mortality rate by prefecture as reported by the Health and Welfare Ministry of Japan [33], Okinawa prefecture shows a specific phenomenon in which the uterine cancer mortality rate (9th ICD-35) is the highest in Japan despite the overall mortality rate being the lowest for both men and women. The reason for this discrepancy is unclear. One possiblity is the difference in the method of tap water treatment between mainland Japan and Okinawa prefecture. In Okinawa, the water supply for many regions was supplemented with fluoride from 1945 to 1972, whereas such fluoridation did not occur in mainland Japan during the same period. Uterine cancer mortality in Okinawa gradually decreased after cessation of fluoridation in 1972 and is currently below the national average in Japan (1991,1992). This fact is considered to support the association between uterine cancer and fluoride. To the best of the present author's knowledge, no other studies have reported such an association. The National Toxicology Program (NTP) studies of conditions associated with a 2-year fluoride supplementation experiment revealed equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of ostrosarcomas in the dosed animals [34]. Furthermore, NTP studies conducted using methodologically acceptable current standards to evaluate the carcinogenicity of fluoride in experimental animals showed that uterine stromal polyps are observed in fewer treated rats than controls. Some species have shown sensitivity to fluoride levels that are higher than those normally encountered. This has resulted in impairment of fertility and reproductive performance [35-37]. Furthermore, fluoride has been reported to inhibit both protein and DNA synthesis in mammalian cells and to induce chromosome aberrations in rodents and human cells in tissue culture [38-41].

However, the carcinogenicity of fluoride in animals and humans remains unclear despite numerous biomedical and epidemiological studies [7, 42-46]. The present study was able to demonstrate a possible association between water fluoridation and uterine cancer mortality. Further research, therefore, will be necessary to evaluate this association. These studies should emcompass other individual predictors of cancer risk (or confounding factors), such as smoking,dietary patterns and sexual activity.

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