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Case-Control Cancer Mortality Study and Chlorination of Drinking Water in Louisiana

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Several Louisiana parishes (counties) using the Mississippi River for their source of public drinking water have the highest mortality rates (1950-69) in the United States for several cancers. Therefore, a case-control mortality study on cancer of the liver, brain, pancreas, bladder, kidney, prostate, rectum, colon, esophagus, stomach, non-Hodgkin's lymphoma, multiple myeloma, leukemia, Hodgkin's disease, lung, breast and malignant melanoma, from 1960 to 1975 in South Louisiana parishes grouped for similarities in industrial characteristics, having approximately equal exposure of the population to surface and groundwater, was conducted. Noncancer deaths were randomly selected as controls and matched to the case death on age, race, sex, and year and parish group of death. Water source at death was assigned based on the residence at death and described as surface or ground and chlorinated or nonchlorinated.

A significantly increased risk for surface, chlorinated water use was noted for rectal cancer. No risk could be demonstrated for colon cancer. The risk noted for bladder cancer by other investigators is not substantiated. Brain cancer risk appears to be associated with chlorinated groundwater, but this may be industrial confounding. Breast cancer demonstrated a slight, but significant, risk associated with surface chlorinated water. This risk, however, might be due to confounding of rural life style, early childbearing and large families with nonchlorinated water found in these settings. Chlorination risk for kidney cancer was not significant. No risk was observed in association with surface water for other cancers of the gastrointestinal or urinary tract. Multiple myeloma was significantly associated with a risk from ground water.

Introduction

Because South Louisiana is an area where comparatively large amounts of organic contaminants have been detected in municipal water supplies and because it is also an area with extremely high mortality rates for cancers of several sites and for all sites combined in selected counties (parishes) which have different sources of drinking water, it was a natural location to investigate what relationship, if any, exists between water quality and cancer incidence (*1–4*). Beginning in 1974 with the draft report released by the Environmental Defense Fund, aggregate studies conducted with Louisiana statistics demonstrated significant associations between cancer mortality and the use of chlorinated surface water (*5*). These results were significant primarily for the urinary tract and gastrointestinal cancers and were race- and sex-dependent, being primarily observed in white males. Bladder cancer in particular showed a strong association with drinking water among white males.

The present study uses the last half of the same data base as used for the aggregate studies and includes 6 later years, but is a case-control mortality study in which the residence and water supply of each decedent was individually linked. The methodology chosen allowed for greater specific control over certain known confounders such as urban or industrial influences, though many lifestyle characteristics were still unknown and therefore uncontrolled. So while this study provides more certainty than the aggregate studies which preceded it, it cannot provide final proof of a

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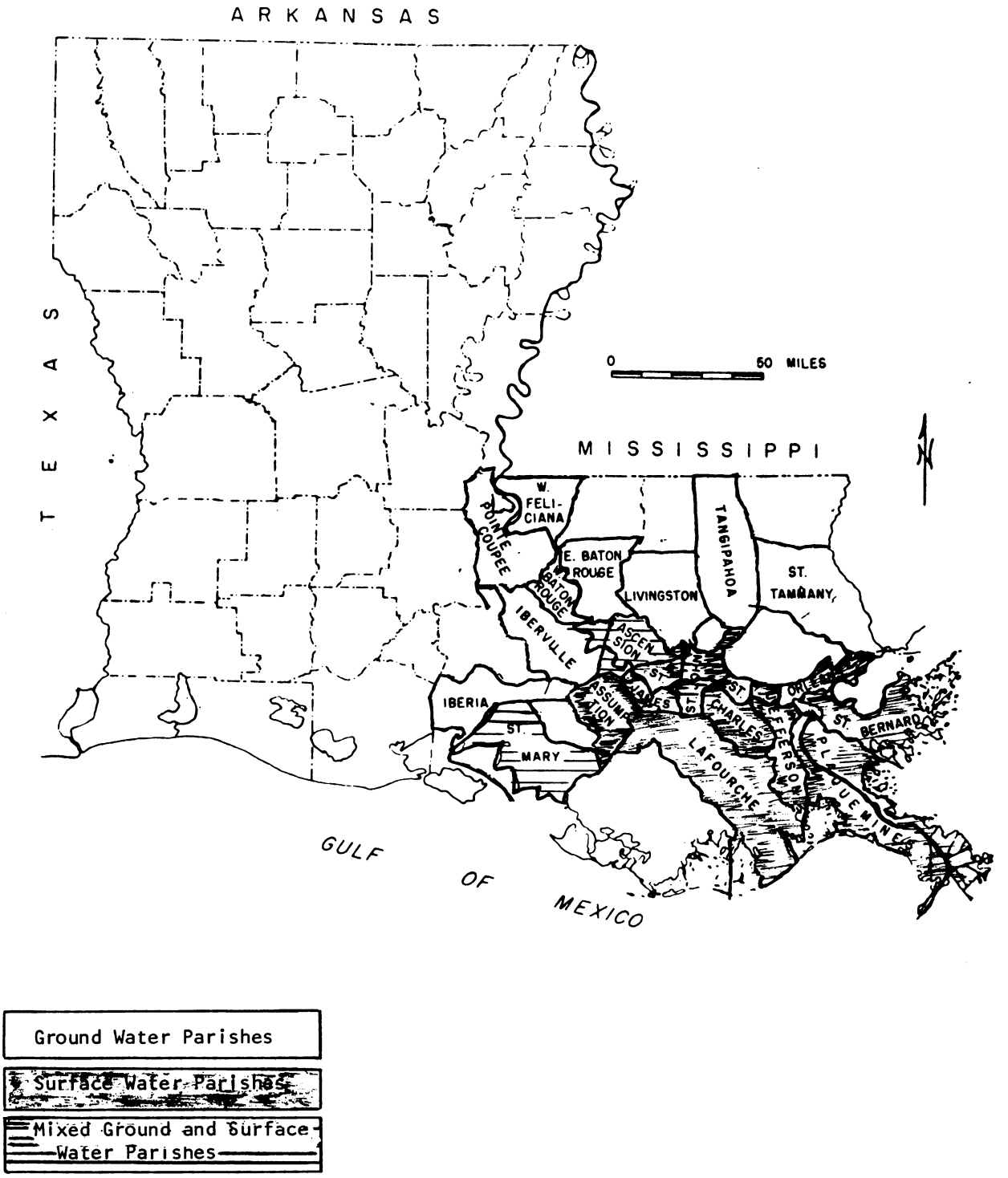

FIGURE 1. Louisiana parishes included in the study and their water source.

drinking water effect on the mortality from any given cancer.

Methods

Figure 1, a map of Louisiana, illustrates the parishes (counties) included in the study and their water source.

As shown in Table 1, 13 parishes (counties) in South Louisiana were combined into groups which were similar in industrial characteristics but contained parishes using ground and surface water in approximately equal proportions. The parish groupings and their 1970 populations are presented in Table 1. Cases were cancer deaths from each of 17 cancer sites, in some of which a drinking water risk was expected and sites where none was expected. Sample size was determined by the magnitude of the expected risk based on the previous studies using aggregate data or by the available population, whichever was smaller. The sample size used for each cancer site is presented in Table 2, with the ICDA numbers which defined the sites used. For the first eight cancer sites, the population used represents all six parish groups, while for the last nine cancer sites only three of the six parish groups were used. The deleted three parish groups together represented only about 20% of the total study population and were methodologically problematic for various reasons. Therefore, they were not included for the second half of the cancer sites.

An equal number of noncancer deaths of the same race, sex, year of death and age as the case were randomly selected from within the noncancer deaths in the parish group in which the case was a resident. Death certificates for all of the cases and controls were abstracted for information on usual occupation and industry and location of residence. Location of the residence at death was used to identify the water company or water source in use at that residence. Water companies supplied service area maps and also indicated which residences utilized private wells. Length of residence at the residence at death was unknown and attempts to determine it through external sources were not uniformly successful.

Table 2 presents the number of cancer deaths in the 13 study parishes between 1960 and 1975 for each of the 17 cancer sites studied. The total number of cancer deaths selected, after sampling Orleans by 1/3, was 19,936. From these, 11,349 were used for the study, which when matched with controls resulted in a total population of 22,698.

The drinking water variables used were acquired from the Louisiana State Office of Health Services and Environmental Quality and reflected the levels available for the water source in use at death and for the years immediately preceding the year of death, going back in time as far as the data permitted. In examining chlorine, the population was trichotomized into those whose water source was nonchlorinated (groundwater), those whose

Table 1. Population resident in study parishes by parish group.

Parish group	Water source	Parish	1970 Pop.	Total
A	Ground	St. Tammany	63,685	
	Surface	Lafourche	68,941	132,626
B	Ground	Iberville	30,746	
		Iberia	57,397	
		Livingston	36,511	
	Surface	St. Charles	29,550	
		St. Bernard	51,185	
		Plaquemines	25,225	
		St. James	19,733	250,347
C	Ground	East Baton Rouge	285,167	
	Surface	Jefferson	337,568	622,735
D	Ground	West Feliciana	11,376	
	Surface	Assumption	19,654	31,030
E	Ground	West Baton Rouge	16,864	
		Tangipahoa	65,875	
		Pointe Coupee	22,002	
	Surface	Orleans (1/3)	197,823	302,564
F	Mixed	Ascension	37,086	
		St. John	23,813	
		St. Mary	60,752	132,626
Total				1,460,953

Table 2. Cancer sites included in the study, total available deaths and sample size.

Cancer site	I.C.D.A. codes		Total no. deaths	Sample size
	7th. revision	8th. revision		
Liver	155.0, 156.1-156.2	155.0-155.1, 197.8, 197.7	696	548[a]
Brain	193.0, 193.9	191.0-192.9	650	611
Pancreas	157	157.0-157.9	1498	980
Bladder	181.0, 181.8	188	759	759
Kidney	180	189.0-189.2	482	440[b]
Prostate	177	185	1400	932
Rectum	154	154.0-154.2	724	692
Colon	153.0-153.9	153.0-153.9	2402	1167
Esophagus	150	150	457	457
Stomach	151	151.0-151.9	1391	700
Non-Hodgkins' lymphoma	200.0-200.2, 202.0-202.1, 205	200.0-200.1 202.0-202.9	538	531
Multiple myeloma	203	203	273	267
Leukemia	204.0-204.4	204.0-207.9	1033	989
Hodgkin's lymphoma	201	201	248	236
Lung and bronchus	162.1, 163	162.1	5221	880
Breast	170	174	1970	968[c]
Malignant melanoma	190.0-190.9	172.0-172.9	194	192
Total			19,936	11,349

[a]Excluding definitely secondary liver.
[b]Excluding Wilms' tumor cases.
[c]Excluding males, in addition to sampling.

water source had a chlorination level below the mean (which was 1.09 ppm) and those whose water source had a chlorination level above the mean. The chlorination level used was measured from the finished water as it left the water treatment plant, rather than as it came out of the tap.

Since it was possible to assign the chlorine variable to only about 80% of the study population, a possibly biased lost-to-follow-up must be considered. In addition, the value was highly associated with year of death, so it is likely that the recording or the use of chlorine changed during the study period. The use of the value recorded at the treatment plant does not capture the loss of chlorine concentration as it travels different distances throughout the supply system. The other way of looking at chlorine level in a more qualitative manner, by separating water source into ground nonchlorinated, ground chlorinated and surface chlorinated, has the advantage of using the total study population and possibly reflecting interactions between contaminants of the surface water source and chlorination. This qualitative distinction will be used to examine any findings which suggest a purely chlorine or chlorine in conjunction with a particular source of water.

In order to evaluate the effect of chlorination on the distribution of cases and controls in the light of other variables which might be significant effect-modifiers, a multidimensional contingency table analysis was performed which was based on the log-linear model and utilized maximum likelihood estimations of all main effects and interactions. This is a BMD package program, P3F (*6*). By using this method of analysis it is possible to see to what extent all main effects are dependent on higher order interactions. All of the matching variables were used as possible effect modifiers in the analysis, with age dichotomised at the mean for the site, and year of death, dividing the study period in halves. Chlorine was trichotomized into none, low or high and its relationship with disease, or case/control, was examined by sex, race, age, and year of death. By using the methodology recommended by Morton Brown, the basic structure of the data was explored by fitting different explanatory models and determining the model with the closest fit (*6*). The first model fit was all of the highest order interactions, and from this all interactions were deleted which did not make a significant contribution to the overall fit. By this process a final model was developed composed of various levels of interactions, which as a whole described the data optimally given the variables. The contribution of each of the terms of the model to the overall fit is estimated by a likelihood ratio chi square.

Results

Table 3 presents the results from the multi-way contingency table analysis for each of the different cancer sites when analyzed with chlorine level. The

Table 3. Summary of multiway contingency table analysis for cancer sites by chlorination of water.

	Chlorination level (none, low or high)		
	Significance level of		
Cancer site	Main effect	Higher order	Significant effect modifiers
Liver	—	—	—
Brain	—	0.008	Race, age, year of death
Pancreas	—	0.047	Race, age, year of death
Bladder	—	—	—
Kidney	—	0.010	Sex, age, year of death
Prostate	—	.045	Race, age, year of death
Rectum	0.012	—	None
Colon	—	—	—
Esophagus	—	—	—
Stomach	—	0.018	Sex, race, age
Non-Hodgkin's lymphoma	—	—	—
Lung	—	—	—
Breast	—	—	None

significance level of the main order effect, of chlorine and disease unmodified by any of the other variables, is presented in the first column. Rectum and breast are the only cancer sites which show a significant main effect. The next column shows the significance level of higher order interactions, in which the correlation of disease and chlorine was dependent on other variables. These other variables, effect modifiers, are listed in the last column. Brain, pancreas, kidney, prostate and stomach show five-way interactions between disease, chlorine and three other variables. Table 4 shows the results for the sites where the qualitative distinction of water source type was used rather than the chlorine level. This was done because of the small sample size of many of these sites. Only malignant melanoma shows a significant higher order interaction in which disease and water source is dependent on sex and age.

Brain cancer showed a highly ($p = 0.008$) significant relationship between disease, chlorine level, race, age and year of death. On examining the distribution it was discovered that there was a chlorine effect but it was seen only among the younger whites. Table 5 shows the distribution of young whites by chlorination level for the first half of the study period and for the last half of the study period. Odds ratios are calculated by comparing each chlorination level to no chlorine. There is a chlorination effect but it is not dose-dependent, that is, the low chlorine level shows more risk than the high chlorine level. The later time period shows a higher risk than the earlier time period. In fact, when this group is analyzed by the contingency table analysis, the main effect between disease and chlorine is significant among this group, although not among the earlier group.

While it is difficult to explain why chlorination would affect whites more than blacks, the association of the risk among those younger than the mean age, which in brain is 46 years, and its appearance in the later time period is cause for concern. While a dose-response relationship would be added validation to this effect, the chlorination level is sufficiently imprecise to understand the lack of such a relationship. When the effect is examined by the qualitative variable of water source type, the risk is found among the ground chlorinated category exclusively

Table 4. Summary of multiway contingency table analysis for cancer sites by type of water source.

	Water source type (surface, ground Chl, ground non-Chl)		
	Significance level of		
Cancer site	Main effect	Higher order	Significant effect modifiers
Multiple myeloma	—	—	—
Leukemia	—	—	—
Young	—	—	—
Old	—	—	—
Hodgkin's lymphoma	—	—	—
Malignant melanoma	—	0.04	Sex, age

Table 5. Distribution of white cases and controls younger than the mean age by chlorination level and year of death and brain cancer.

Chlorination level	Year of death < 1969			Year of death ≥ 1969		
	Cases	Controls	O.R.[a]	Cases	Controls	O.R.[a]
High chlorine (> 1.09)	23	14	1.73 (0.64-4.70)	25	18	1.97 (0.68-5.72)
Low chlorine (≤ 1.09)	33	19	1.82 (0.73-4.56)	23	7	4.65 (1.34-16.89)
No chlorine	20	21	—	12	17	

[a]Odds ratio between each category and no chlorine.

and not among the surface chlorinated. In addition to these results with water an analysis of occupation turned up a significant risk for brain cancer in chemical workers, with a lower mean age in these cases (51 years) than in the controls (62 years) who worked for chemical plants. Since the Baton Rouge area has many chemical and petrochemical industries, and is also the largest area using ground chlorinated water in this study, it may be that this chlorine effect is actually due to confounding with occupation. This could explain the fact that the effect is seen only among whites and may represent an occupational bias.

In pancreatic cancer, the multidimensional contingency table analysis uncovered a five-way interaction between disease, chlorine, race, age and year of death. On examining these effects in detail the interaction term, which was only of borderline significance, represented an extremely inconsistent pattern. Risks for both nonchlorination and for high chlorination were seen in different cells of the table, with no consistent trend in other cells. On balance it appears that no association of pancreatic cancer and chlorination level is demonstrable from these data.

Bladder cancer showed no relationship with chlorination or with any of the other water variables. However, because of the results of the Environmental Defense Fund report in 1974, where a significant water effect was observed for white males, the data was examined more closely to see if an effect could be detected. In Parish Group B, consisting of rural parishes above and below the Mississippi River from New Orleans (Orleans, Jefferson and St. Bernard Parishes), there was a highly significant surface water risk among white males, as seen on Table 6. The number of parishes involved in this risk is large, though the population of the parishes is small. In a multiple regression procedure with each parish contributing equally, the effect of these parishes is much larger than in a methodology based on individuals and their water source. It is possible that the pattern seen in these parishes may have been overemphasized by the method of analysis chosen previously. It appears

Table 6. Distribution of bladder cancer cases and controls by parish in parish group B white males.[a]

Water source	Parish	Cases	Controls
Ground	Iberia	9	17
	Iberville	10	10
	Livingston	14	22
	Total	33	49
Surface	Plaquemines	6	2
	St. Bernard	13	7
	St. Charles	8	4
	St. James	4	2
	Total	31	15

[a]Odds ratio (surface to ground): 3.07; $p < 0.01$.

unlikely that there is a surface water contaminant in the water above and below New Orleans but not in New Orleans, which only affects white males. This result is likely to be one of the random significances one expects to see in subsets of a large data set, or confounding associated with another environmental factor.

Kidney cancer also showed a highly significant five-way interaction between disease, chlorine, sex, age and year of death, but on examination of specific cells, this too was discovered to represent an inconsistent pattern. The only significant risk seen was for nonchlorination among older males dying in the earlier half of the study period.

Although a slight risk for chlorination was observed in all of the other cells of the table, this risk was not sufficiently pronounced to be significant. Prostate showed the same pattern of inconsistencies between cells of the table, with the only significant risk being for no chlorination among young whites dying in the earlier half of the study period.

With rectal cancer, however, there is a significant main effect between disease and chlorine which is not dependent on any of the other variables in the model. Table 7 shows the distribution of the cases and controls by chlorination level, with the odds ratio of each chlorination category compared with the nonchlorine category. There is a dose-response

Table 7. Distribution of rectal cancer cases and controls by water source type and chlorination level.

Chlorination level	Cases	Controls	O.R.[a] (95% C.I.)	Water source type	Cases	Controls	O.R.[a] (95% C.I.)
High (> 1.09 ppm)	176	135	1.68 (1.17-2.42)	Sur, Chl.	462	396	1.53 (1.15-2.04)
Low (≤ 1.09 ppm)	274	275	1.29 0.93-1.79)	Gnd, Chl.	106	134	1.04 (0.72-1.50)
No	96	124		Gnd, Non-Chl.	116	152	
Total	546	534		Total	684	682	

[a]Odds ratio between each category and no chlorine.

Table 8. Distribution of rectal cancer cases and controls by chlorine level for those on surface water.

Chlorination level	Surface water Cases	Surface water Controls	O.R.[a] (95% C.I.)
High (> 1.09 ppm)	175	133	1.12 (0.81-1.55)
Low (≤ 1.09 ppm)	181	154	
Total	356	287	

[a]Odds ratio of high to low chlorine.

Table 9. Distribution of rectal cancer cases and controls by water source for those on low chlorine.

Water source type	Low chlorine Cases	Low chlorine Controls	O.R.[a] (95% C.I.)
Surface	181	154	1.53
Ground	93	121	(1.07-2.19)
Total	274	275	

[a]Odds ratio of surface to ground.

relationship, with the low chlorine showing less of a risk than the high chlorine category. When this same relationship is examined using the qualitative variable of water source type, however, it is clear that the difference is found mostly between surface and ground water, since there are more controls than cases in the ground chlorinated category.

Because surface water source and heavy chlorination are so closely related it is difficult to distinguish between their effects. However, one can first control for chlorination and look at residual risk for water source, and similarly control for water source and look at residual risk for chlorination. In the surface water category there is some variability in the level of chlorination, and Table 8 shows the distribution of cases and controls by chlorine level among those on surface water. While there is a slight increased risk in the high chlorine category, this increase is not statistically significant. The surface water effect among those in the low chlorine category is presented in Table 9 and demonstrated that there is still a significant surface water effect after controlling for chlorine level, though it is less than it was when not controlling for chlorination.

Because controlling for water type diminishes the risk for chlorine and controlling for chlorine diminishes the risk for surface water, it is likely that both are necessary for the large increased risk seen for chlorinated surface water. This is, of course, an intuitively attractive hypothesis since the potential for damage from chlorination is so much greater if the water is heavily contaminated with organics before being chlorinated. While it is methodologically impossible to separate heavy chlorination from surface water source in South Louisiana, it is clear that whether it is due to the chlorination per se or to the chlorination added to contamination, the surface chlorinated water of South Louisiana is definitely associated with a significant risk for rectal cancer.

No risk whatsoever was observed with colon cancer, in contrast to rectal cancer, though control selection and data processing for these two sites were done simultaneously. The fact that colon cancer does not associate with drinking water at all though it is known to be highly correlated with lifestyle factors such as diet, supports the assumption that in fact the methodology used for this study was successful in controlling for these other factors.

Stomach cancer also showed a five-way interaction between disease, chlorine, sex, race and age. This was found to consist of a risk for high chlorine among older white males, but no such risk was detected in the other cells of the distribution and therefore was judged to be inconsistent. No chlorine effect was observed with lung or with non-Hodgkins' lymphoma.

Breast cancer, however, showed a significant main effect between chlorine level and disease. The distribution of cases and controls is presented in Table 10 along with the odds ratio between each

Table 10. Distribution of breast cancer cases and controls by chlorination level.

Chlorination level	Cases	Controls	O.R.[a] (95% C.I.)
High chlorine (> 1.09 ppm)	309	294	1.58 (1.09-2.29)
Low chlorine (≤ 1.09 ppm)	489	457	1.61 (1.13-2.30)
No chlorine	64	96	
Total	862	847	

[a]Odds ratio between each category and no chlorine.

category and the no chlorine category. As is seen from the table, the risk for low chlorine is higher than the risk for high chlorine, though both are significantly greater than one. On close examination of this risk, however, it was discovered that it was not found in the parish group consisting of Baton Rouge and Jefferson parishes, two urban parishes comprising the same parish group. That is, in the parish group where urban lifestyle was the most successfully controlled, the risk disappeared. Following that observation, the other parish groups were closely examined to see whether the observed risk might be reflecting an urban area with chlorine matched with more rural nonchlorinated areas. Through detailed examination of the actual residence of the cases and controls it was determined that such confounding might possibly have been responsible for the observed effect. Since small family size is a risk factor for breast cancer and an attribute of urban living such confounding could have resulted in an apparent risk for chlorination.

The cancer sites which were examined by using the water source type variable showed no association between disease and water, except for malignant melanoma, where there was a risk still dependent on sex and age. This consisted of a risk for ground water among older females, a risk which was not reflected in the other cells of the table.

Discussion

In conclusion, then, there is a definite association between chlorinated surface water and rectal cancer, with a risk of about 2 for those living on the chlorinated surface water. This risk is not sex- or race-dependent, or dependent on any of the other variables in the model. In results reported elsewhere (*7*), it was also shown that this risk increased as one approached the mouth of the Mississippi River and increased with increased duration of use. In contrast to this, colon cancer showed no association with any water variable. Rectum is a logical target site to demonstrate this effect due to its physiologic function.

The apparent main effect with breast cancer and chlorinated water may be due to confounding of small family size with chlorinated water, though it might also be a valid water association. The fact that it is not present in the parish group made up of the two urban parishes raises questions about the observed effect. The association of brain cancer with chlorine is also questionable, since it is present only among whites and primarily in the Baton Rouge area, where there are many chemical plants. Association between chlorination and other sites of cancer are heavily dependent on the matching variables of race, sex, age and year of death and the effects observed were not found to be consistent in any way which would suggest a true drinking water effect.

While those apparent effects appear to be nonsubstantial, the results with bladder show a clear lack of drinking water effect though there is a risk for drinking surface water in one parish group in one race/sex category. Since the risk seen is from parishes above and below New Orleans, but not in the New Orleans area itself, it is unlikely to be a drinking water risk, but more likely an industrial risk.

Therefore, there appears to be some risk associated with water chlorination, although some definitive and specific studies must be undertaken especially with regard to the importance of co-contaminants and possible industrial confounders. Recently reported similar observations by Kanarek and Young with regard to colo-rectal cancer and chlorinated drinking water are supportive of these observations (*8*). Although the risk for colon cancer was not observed in this study, this could be attributed to methodologic differences.

The fact that only rectal cancer demonstrates this association even on such a survey study as this, is likely an indication of risk to other organ sites which a more definitive study is necessary to demonstrate.

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REFERENCES

1. Dowty, B. J., Carlisle, D. J., and Laseter, J. L. New Orleans drinking water sources tested by gas chromatography-mass spectrometry. Environ. Sci. Technol. 9: 762-765 (1975).
2. Dowty, B. J., Carlisle, D. J., and Laseter, J. L. Haloge-

nated hydrocarbons in New Orleans drinking water and blood plasma. Science 187: 75-77 (1975).
3. Mason, T. J., and McKay, F. W. U.S. Cancer Mortality by County: 1950-1969. DHEW Publication No. (NIH) 74-615, Washington, D.C., 1974.
4. Mason, T. J., McKay, F. W., Hoover, R., Blot, W. J., and Fraumeni, J. F., Jr. Atlas of Cancer Mortality for U.S. Counties: 1950-1969. DHEW Publication No. (NIH) 75-780, Washington, D.C., 1975.
5. Harris, R. H. The implication of cancer-causing substances in Mississippi River water. Environmental Defense Fund, Washington, D.C., 1974.
6. Brown, M. B. Screening effects in multidimensional contingency tables. Appl. Statistics 25: 37-46 (1976).
7. Gottlieb, M. S., Carr, J. K., and Morris, D. T. Cancer and drinking water in Louisiana: colon and rectum. Internatl. J. Epidemiol. 10: 117-125 (1981).
8. Kanarek, M. S., and Young, T. B. Drinking water treatment and risk of cancer death in Wisconsin. Environ. Health Perspect. 46: 179-186 (1982).