APPENDIX E

FLUORIDATION OF DRINKING WATER AND SUBSEQUENT CANCER INCIDENCE AND MORTALITY

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INTRODUCTION

For over 40 years, fluoridation of municipal drinking water supplies to prevent dental caries has sparked controversy. The issues involved have been political and public policy in nature, with claims of possible health effects sometimes evoked to buttress the arguments. Among the many adverse effects raised by opponents of fluoridation as being possibly related to fluoride ingestion is the risk of malignancy. For this reason, the relationship between natural and artificial fluoridation of drinking water and cancer incidence and mortality has been the subject of numerous epidemiologic studies. These investigations, employing a variety of methods, have been conducted in many regions around the world. The results have been intensively reviewed by a number of expert panels (1-3), and the conclusions reached have been remarkably consistent. That is, when appropriate methods are applied to high-quality data, the resulting analyses have not found any evidence of an association between fluoridation of drinking water and an increased risk of cancer.

In March of 1990, a preliminary report of a bioassay study conducted in rodents under the auspices of the National Toxicology Program suggested a relationship between the dose of fluoride and the risk of osteosarcomas and possibly the risk of oral tumors (4). The Draft Technical Report (5) prepared subsequently for a peer review committee concluded that: "Under the conditions of these 2-year dosed water studies, there was equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals. There was no evidence of carcinogenic activity in female F344/N rats receiving sodium fluoride at concentrations of 25, 100, or 175 ppm (11, 45, or 79 ppm fluoride) in drinking water for 2 years. There was no evidence of carcinogenic activity of sodium fluoride in male or female mice receiving sodium fluoride at concentrations of 25, 100, or 175 ppm in drinking water for 2 years." The suggestion of a relationship with oral cancer was discounted in this report: "The squamous cell neoplasms in rats receiving sodium fluoride were not considered chemical related because a squamous cell carcinoma was observed in one control male (paired control group) and in one control female, the incidence rates in the dosed groups were not significantly greater than in concurrent controls and were within the range of historical controls, and there was no supporting evidence of focal hyperplasia of the oral mucosa."

In 1976, the National Cancer Institute (NCI) evaluated 20 years of U.S. cancer mortality and a limited amount of cancer incidence data, and found no pattern consistent with an adverse effect of fluoridation (6). In the face of the new laboratory findings, we felt it was appropriate to update this study. The passage of time has provided 16 additional years of mortality data, enabling an evaluation of the effects of up to 35 years of fluoridation. In addition, the establishment in 1973 of the NCI Surveillance, Epidemiology and End Results (SEER) program, a network of population-based cancer incidence registries, has resulted in more relevant incidence data than were previously available. Incidence statistics are especially important for the evaluation of bone osteosarcoma, since histology-specific information is not generally available in mortality data. In addition, mortality data for bone cancer are limited since bone is a frequent site of metastases for a number of common malignancies, which may be misclassified as bone cancer deaths.

MATERIALS AND METHODS

Population-based cancer incidence data for 1973-87 were obtained from the nine registries participating in the SEER program (7). This program provides continuous incidence coverage for about 10% of the U.S. population. National mortality data from 1950-85 were obtained from the Center for Health Statistics, and populations at risk were estimated based on decennial censuses conducted by the Census Bureau (8).

Data regarding fluoridation of municipal water supplies and levels of natural fluoride were based on records from a series of published fluoridation censuses provided by the Centers for Disease Control (CDC) (9-12). The communities served by these water systems were identified and their populations related to the total population of the counties in which they were located. The listings of counties were reviewed with the assistance of the CDC, then modified, and finally validated by state public health or drinking water supply officials. The proportion of each county's population that received fluoridated water was used to categorize counties as non-fluoridated (control or non-exposed), fluoridated (exposed), or out-of-scope (not qualifying as a fluoridated or non-fluoridated county). A small proportion of the digitized records of the 1985 Fluoridation Census, from which our lists were first generated, do not include populations of served communities. While we made extensive efforts to complete this information, it is possible that a small number of fluoridated counties which should have been included in our analysis were inadvertently omitted. However, even if this occurred, it would not have biased the results of the analyses.

For the mortality analysis, we focused attention on areas likely to have centralized water systems, and thus we included only those counties that were more than 50% urban in 1980. Due to difficulties in county definitions, we excluded Alaska, Hawaii, and Virginia from the analysis. A county was considered exposed if the proportion of the population served by fluoridated water increased from no more than 10% to more than two-thirds within a three-year period. Control counties were those with no more than 10% of the population through 1985 ever served by artificially-fluoridated water or by water that was naturally fluoridated above 0.3 ppm. The mortality analysis thus is based on 131 fluoridated counties with a 1980 population of 40,362,091 persons, accounting for 22% of the U.S. population, and 195 non-fluoridated counties with a population of 30,216,689, accounting for 13% (Appendix Table E).

Since many fewer counties were available for the incidence analyses, slightly more liberal criteria were used for defining exposure. Selection was not limited to counties that were >50% urban. Levels of natural fluoride were not considered. This is reasonable since the evaluation was based entirely on time trends--an analysis that would be sensitive to changes in fluoridation and not influenced by the baseline levels. Finally the proportion of the population served that would qualify it as an exposed county was lowered to 60%. Thus, for the incidence analysis, a county was considered exposed if the proportion of the population served by artificially-fluoridated water (usually about 1 ppm) increased from no more than 10% to more than 60% within a three-year period. If fluoridation occurred over more than one year, the single year that the largest proportion of the population was affected was used as the index year for fluoridation. Control counties were those with less than 10% of the population ever served, through 1987, by artificially-fluoridated water. Counties which did not meet the criteria for being either fluoridated or non-fluoridated were excluded from the study. Seven of the nine SEER areas had inadequate variation in fluoridation exposure levels to allow for meaningful analysis. Two SEER areas, Iowa and the Seattle metropolitan area, included both fluoridated and control counties: 11 exposed and 14 non-exposed counties in Iowa, and one exposed and seven non-exposed counties in Seattle (Appendix Table A). Incidence data for 1973 were not available for the Seattle area, as the registry commenced operation in 1974.

Our study was restricted to the white population to avoid confounding by the substantial racial variation in cancer incidence and mortality rates (13). Definitions of the groupings of cancers are presented for the incidence analysis in Appendix Table B and for the mortality analysis in Appendix

Table F. Major emphasis was placed on changes in cancer risk relative to the time of fluoridation in those counties that were artificially fluoridated, comparing ever-fluoridated with never-fluoridated counties for baseline purposes only. Observed cases (or deaths) in fluoridated counties were compared to those expected based on age-, sex-, time-, and region-specific rates in non-fluoridated counties. These were aggregated into five-year periods relative to time of fluoridation, and the ratio of observed-to-expected (O/E) events was then calculated (14). Poisson regression models were used to estimate corresponding relative risks (RR), 95% confidence intervals (CI), and the significance of trends in RRs according to duration of fluoridation (15,16). For the Poisson analysis, data were cross classified by county, year (1973-77, 78-82, 83-87), age (0-4, 5-9 ..... 85+), sex and time since fluoridation (never, 0-4, 5-9, 10-14, 15-19, $\geq$20). The mean duration of fluoridation within each cell was used as the quantitative value for the trend tests. All regression analyses controlled for categories of age and year, at least, and for area and sex where appropriate.

RESULTS

INCIDENCE ANALYSIS

Bone Cancer: Table 1 presents the observed numbers of incident cancers of the bones and joints and the subset of osteosarcomas occurring in fluoridated counties of the Iowa and Seattle SEER areas, and the O/E ratios based on expected values generated from the age-, sex-, time-, and area-specific rates in the non-fluoridated counties. The O/E ratios are presented by duration of fluoridation from <5 years through $\geq$20 years. Overall, the risks in fluoridated and non-fluoridated areas were quite similar. A total of 290 cases of bone and joint cancer occurred in fluoridated areas compared to 279 expected based on the rates in non-fluoridated areas. The comparable numbers for osteosarcomas were 91 observed and 93 expected. There were no patterns in the O/Es by interval from fluoridation that suggested an effect either in the total group or in men and women separately. The O/E ratio was slightly higher in the <5 year interval from fluoridation for bone and joint cancers, based on nine observed cases of osteosarcoma vs. 4.89 expected. While examination of patterns in each of the two areas was hampered by small numbers, all nine cases were observed in Seattle compared to 2.91 expected during this short interval from fluoridation.

The categorization of duration of fluoridation was revised for cancers which have a substantial childhood component, such as bone malignancies. Obviously, for example, in counties fluoridated for 20 or more years, individuals under 20 years of age could not attain 20 years of exposure. Thus for bone malignancies and osteosarcomas, the observed and expected numbers were also classified by duration of fluoridation or age, whichever was less. The results of this analysis resembled the patterns seen in Table 1. For all bone and joint cancers, the O/Es by duration of fluoridation were 1.3, 1.0, 1.1, 1.1, and 0.9 for <5, 5-9, 10-14, 15-19 and 20+ years, respectively. For osteosarcomas, the corresponding O/Es were 1.8, 1.0, 0.8, 1.0, and 0.9. Because of the age curve for these tumors and the timing of fluoridation, we also compared the incidence among those under age 30 who resided in counties with fluoridated water for their entire lifetime to the incidence among those exposed for only part of their life. Using this approach, the observed number of bone and joint cancers among those with lifetime exposure was 77 compared to an expected value of 58.16 based on age-, sex-, time- and area-specific rates in the non-fluoridated counties (O/E=1.3). Among those exposed less than one-half of their life, the observed number was 23 compared to an expected of 23.11 (O/E=1.0). While this ratio was slightly lower than that for the group with lifetime exposure, the two O/Es were not significantly different from one another (95% confidence interval for the O/E of 1.0 is 0.6-1.5). The observed and expected values for osteosarcoma associated with lifetime exposure were 30 and 32.65 (O/E=0.9), while the corresponding values associated with less than one-half lifetime exposure were 10 and 11.15 (O/E=0.9). Thus, these results do not provide any evidence of an adverse effect of fluoridation on the risk of bone tumors.

While not under *a-priori* suspicion, other histologic types of bone cancer were also evaluated for their relationship to timing of fluoridation. There was an excess of Ewing's sarcoma in the fluoridated

counties (observed = 49, expected = 30.33, O/E=1.6). Virtually all of this excess was derived from the 20+ years of fluoridation category, where 16 cases were observed versus 1.64 expected (O/E=9.8). Upon further evaluation, it was noted that the expected value for the 20+ year category was extremely unstable, since the rate used to generate it was based on only one case occurring in the non-fluoridated portions of Iowa during the relevant time period. The question arose as to whether there was a real excess, or whether the rate of this rare tumor was low simply by chance in the relatively small population of the non-fluoridated portions of Iowa during this time. To address this issue, we expanded the comparison population by adding to the non-fluoridated counties in Iowa all counties in the rest of the SEER program where less than 10% of the population was exposed to artificially or naturally fluoridated drinking. When the resulting rates were applied to the person-years in the 20+ years-of-fluoridation category, the expected value was 20.45, yielding an O/E ratio of 0.8. Thus, the early observation of an excess of Ewing's sarcoma associated with 20+ years of fluoridation appears to be an artifact due to chance based on an unstable rate in the initial comparison population.

Oral Cancers: Table 2 gives the observed numbers of malignancies of the oral cavity and pharynx occurring in fluoridated counties and the corresponding O/Es by duration of fluoridation for the Iowa and Seattle SEER areas. In Iowa, the observed number of cases in counties fluoridated less than five years was 1.2 times that expected based on the rates in the non-fluoridated counties. The ratio rose to 1.4 in counties fluoridated for 5-9 years, 1.7 for 10-14 years, and 1.6 for the longer intervals. The increase in O/E followed by a plateau reflected the experience of males, which showed a rise from 0.8 in the shortest interval to about 1.6 for each of the longer duration categories. There was no discernable trend among females.

In the Seattle area, no consistent patterns were noted. Overall, the O/Es were 1.0, 1.2, 1.2, and 0.8 for the four duration categories available, and the variations were similar for males and females.

Other Cancer Sites: A series of anatomic sites commonly used in describing cancer patterns was examined for trends by duration of fluoridation. Attention was initially centered on sites for which the expected rates for each sex and duration-of-fluoridation category were based on at least 50 cases. The O/Es were evaluated to 2 decimal places, and are given in Appendix Table C. All other cancer sites were evaluated to one decimal place, and the results given in Appendix Table D.

Only one site, renal cancer [including cancers of the renal parenchyma (kidney) and pelvis], suggested a consistent relationship with duration of fluoridation over the entire time period. In Iowa, the O/E for renal cancer rose from 0.9 in the <5 year category, to 1.0 for the next three intervals, to 1.2 for the 20+ year category. In Seattle, the O/E rose from 0.8 in the <5 year category, to 0.9 in the next two intervals, to 1.1 in the longest category (15-19 years). The sex-specific data were much more variable. An increasing trend with duration was seen only among males in Iowa. However, the highest O/E occurred in the longest fluoridation category for three of the four area-sex groupings (the exception being females in Seattle).

While renal cancer was the only site indicating the need for more detailed analysis, it was recognized that we may be looking for a low-level risk and that we needed to maximize our opportunities to detect one. Therefore, we developed some liberal guidelines in selecting cancer sites to investigate further. We chose any site showing an increasing O/E trend (including ties) with increasing duration of fluoridation for any two of the six area-sex analyses (two of the two for sex-specific sites) in Appendix Tables C and D. Also included were cancer sites where the highest O/E (including ties) occurred in the longest duration-of-fluoridation category in both geographic areas for the same sex group. This resulted in the inclusion of five additional sites for more detailed analysis: cancers of the colon and rectum, soft tissue, prostate, and urinary bladder, and non-Hodgkin's lymphoma. The weakest evidence in this group was for prostate and bladder cancers. For prostate cancer, there was no consistent trend in either Iowa or Seattle; the highest O/E occurred in the longest duration-of-fluoridation categories in both areas, but in each instance, this was by one-hundredth of the O/E ratio (Appendix Table C). For bladder cancer, there was an increasing trend in the O/E for males

in Iowa, ranging from 1.0 in the <5 year interval to 1.2 in the 20+ year group (Appendix Table D). No other area-sex group showed a consistent trend, but for males in Seattle the highest O/E was in the longest duration category. However, this O/E was 1.0, which is identical to the ratios seen in two of the three other duration categories.

For cancers of the colon and rectum, the O/E in Iowa was highest in the longest duration category for both sexes combined, resulting primarily from an upward trend among males. In Seattle, the highest O/E for both sexes combined also occurred in the longest interval, although the ratio (1.03) was identical to that seen in two previous duration categories. For soft tissue cancer, the O/Es in Seattle increased with duration of fluoridation for both sexes combined. This was due to the trend among females, which rose from 0.7 in the <5 year interval to 1.7 in the 15-19 year group. However, no increasing trends were seen among males in Seattle or among any groups in Iowa. In addition, the highest O/E in these groups did not occur in the longest duration category, and some suggestion of an inverse trend was seen among females in Iowa. For non-Hodgkin's lymphoma, the O/Es for the combined sexes in Seattle increased from 1.0 in the <5 year interval to 1.2 in the 15-19 year interval. The trend was apparent among females only, although in males the highest O/E (1.1) was in the longest duration category. In Iowa, no increasing trends were noted with duration of fluoridation in any group, and the O/Es for the 20+ year category were all less than or equal to the O/Es for the <5 year category.

For the sites of *a-priori* interest and for the six sites chosen for further analysis, Poisson regression analyses were performed to estimate risk ratios (RRs) by duration of fluoridation after control for age, sex, calendar time, and geographic area. Data from all of the fluoridated and non-fluoridated counties in the study were used, and for all of the RRs the referent category was an RR of 1.00 in the non-fluoridated counties. Ninety-five percent confidence intervals were calculated for each RR and a test for trend in the ordered RRs was performed. The confidence intervals are useful in several ways. If they exclude 1.0, then a test of the hypothesis that the rates are the same as the referent rates in the non-fluoridated counties would likely be rejected at the $p<0.05$ level. In addition, whether or not the confidence intervals encompass the point estimate for another category is a conservative indication of the possibility that chance events may have accounted for differences between the point estimates of the RRs for these categories. For example, the difference between the RRs for the 20+ year fluoridation category and the <5 year category could more readily be due to chance if each confidence interval includes the other point estimate.

The lack of any consistent pattern for all bone and joint cancers and for osteosarcomas by duration of fluoridation was also seen with the Poisson regression analysis (Table 3). There was no consistent pattern in the RRs by duration of fluoridation for either sex or in the combined data. Not only were there no consistent associations or patterns, but also there were no statistically significant trends in the RRs. In addition, the confidence intervals for the longest duration category in every instance encompassed both 1.00 and the point estimate of the RR for the <5 year category.

For cancers of the oral cavity and pharynx, the overall patterns, as well as the RR point estimates themselves, are quite similar to the O/E ratios (Table 4). In Iowa, the RRs for males and the sexes combined were lowest in the shortest duration-of- fluoridation category, and then increased to around 1.6 for each of the subsequent intervals. The confidence interval for the shortest duration group among males in Iowa excludes the point estimates of each of the subsequent categories and vice-versa. Conversely, in Seattle, the RRs were lowest in the longest duration-of-fluoridation category for males, females, and both sexes combined. The only significant trend in the ordered RRs was the negative trend ($p=0.02$) for the combined sexes in Seattle. Trends of borderline significance ($0.05\leq p<0.10$) in opposite directions occurred for males in Iowa (positive trend, $p=0.05$) and Seattle (negative trend, $p=0.09$). As can be seen from the distribution of the RRs, the statistical significance of these trends was derived primarily from the difference between the value of the RR in an extreme duration category compared to all of the others, rather than from a consistent trend or gradient.

For renal cancer, the only site in the initial analysis suggesting any consistent evidence of a trend in O/E ratios, the patterns of the RRs and their values (Table 5) are similar to those for the O/E ratios. The RRs for both sexes combined in Seattle rose slightly from 0.9 to 1.0, a trend that was statistically significant (p=0.04). None of the other trends was significant, and for each registry-sex category, the confidence interval in the <5 year category included the point estimate of the risk for the longest duration category.

Table 6 gives the modeled RRs by registry and sex for the two more common cancers chosen for further evaluation from the O/E analyses. For colorectal cancers, the results are essentially the same as the O/E analysis. In Iowa, there was a significant upward trend in the ratios with increasing duration of fluoridation, for the sexes combined and among males. In Seattle, the highest ratio occurred in the longest duration category, but the difference was not statistically significant and there was no evidence of a consistent trend. For prostate cancer, the modeled estimates are similar to the O/E ratios except for the 15-19 year interval in Seattle (O/E=1.02, RR=1.13). For both registries, the trends in risk ratios were statistically significant.

Similar analyses for the less common sites are presented in Table 7. In general, the RRs are similar to the O/E analysis. For cancers of the urinary bladder and soft tissue, there were no significant trends with duration of fluoridation, and the confidence intervals for the shortest intervals included the RRs for the longest intervals. For non-Hodgkin's lymphoma in the Seattle registry, the p-value for trend for the sexes combined was 0.01, and the confidence interval around the RR for the 15-19 year interval did not include the RR for the <5 year interval. Among females, the trend was not significant, but the RRs for the longest and shortest intervals were significantly different from each other.

Time-Specific Analyses: For each of the six cancer sites selected for further analyses on the basis of O/E trends, or the presence of the highest O/E in the longest duration-of-fluoridation category in both geographic areas for the same sex, the consistency of these patterns was evaluated by assessing them for two separate time periods (1973-80 and 1981-87). In Iowa, this is an informative test for consistency of associations, since there are a number of fluoridated counties that contribute differentially to the various intervals of fluoridation in these two time periods. For completeness, these time-period data are presented for Seattle also. However, since there is only one fluoridated county in the Seattle registry, separation of the data by time period does not result in a different mix of counties in each grouping but is simply a finer breakdown of duration of fluoridation (i.e., the 10-14 year interval for 1973-80 is actually year 10, and the 10-14 year interval for 1981-87 corresponds to years 11-14).

For renal cancer, the consistent increase in O/E ratios with duration of fluoridation observed in the aggregate data for both sexes combined in Iowa and Seattle, and for males in Iowa, was not seen in any of the nine location-sex-time groupings where trends can be evaluated (those that have data for more than two categories) (Table 8). Indeed, the highest O/E (including ties) occurred in the longest duration-of-fluoridation category in only four out of all 12 groupings. This would have been expected to occur by chance alone about four times, given the number of categories involved in Table 8.

Table 9 presents the time-specific data for the two common cancer sites that warranted further analysis. In the aggregate (1973-87) data for colorectal cancer, the highest O/E ratio occurred in the longest duration-of-fluoridation category (with ties) for the sexes combined in both areas, and there was also a consistently increasing trend in the O/E ratios for males in Iowa. When data are examined by time period, this same pattern prevailed during 1973-80. However, there was no consistent trend during 1981-87 for the sexes combined or for males in Iowa, and in neither instance was the O/E ratio highest in the longest duration category. The O/E for the 15-19 year interval in Seattle was higher than that for 10-14 years, but only marginally so (one-hundredth of the O/E ratio). In the aggregate (1973-87) data for prostate cancer, the O/E ratio was highest in the most extreme duration category for both geographic areas, but the differences were very small. In the time-specific data, this pattern was not seen for either Iowa or Seattle in the earlier period, or for Iowa in the later period.

Table 10 presents corresponding data for the less frequent sites singled out for further analysis. For bladder cancer, the increasing O/E trend among males in Iowa in the overall data was not present in either time period, and only in the earlier period was the highest O/E ratio seen in the longest duration category. In Seattle, where the highest O/E ratio was in the longest interval for males in the aggregate data, the ratio for the longest interval was lowest in the earlier period and highest only in the later period.

For soft-tissue cancer, the O/E increased with duration of fluoridation for both sexes combined in Seattle, which was derived from the trend for females. The trend for the sexes combined was seen in both time periods. However, there was no consistent trend among females in the earlier time period, although in the later period the O/E ratio for 15-19 years was higher than that for 10-14 years. Similar patterns in the overall data were noted for non-Hodgkin's lymphoma (trends in both sexes combined and females, in Seattle only). In addition, the ratio among males in Seattle was highest in the longest duration category. In the time-specific data, the trend for the sexes combined was not seen in the earlier period, but the O/E ratio for 15-19 years was higher than that for the 10-14 category (1.2 vs. 1.1) in the later period. The trend toward increases in O/E ratios for females in Seattle was seen in both time periods.

Thus, for the few cancer sites with any suggestive overall patterns in O/E ratios, the trends were either absent or not consistently seen when examined within separate calendar-time periods. The only exceptions were for soft tissue cancer and non-Hodgkin's lymphoma among females in Seattle. For both soft tissue cancer and non-Hodgkin's lymphoma, there was actually some suggestion of a negative association (lower O/E ratios with longer duration of fluoridation) among females in Iowa.

MORTALITY ANALYSIS

Bone cancer: Table 11 gives the observed numbers of deaths ascribed to malignancies of the bones and joints from 1950-1985 in counties having undergone rapid fluoridation, and O/E ratios based on expected values generated from the age-, sex-, time-, and region-specific rates in non-fluoridated counties. These data are presented in intervals according to time of fluoridation, ranging from 31-35 years prior to fluoridation to 30-35 years post-fluoridation. Overall, 12,363 deaths were observed compared to 12,130 expected. There were no apparent trends that might relate to fluoridation. The highest O/E ratio for males (1.29) occurred 15-19 years post-fluoridation, but ratios for the subsequent 15 years resembled those for the 15-year interval preceding fluoridation. The highest O/E ratio for females (1.30) occurred 16-20 years prior to fluoridation, while the ratios for 20-35 years post-fluoridation were similar or lower than those for the 15-year interval preceding fluoridation.

Oral Cancers: Table 11 also displays mortality data from cancers of the oral cavity and pharynx. Among males, the observed mortality generally ranged from 30 to 50 percent above the expected values, but this applied to the years prior to fluoridation as well as to those afterward, without any evidence of a trend. Females also showed elevated O/E ratios of around ten to 30 percent that were similarly unrelated to the timing of fluoridation.

Other Cancer Sites: Appendix Table G presents the observed deaths and O/E ratios in relation to time of fluoridation for the remaining cancers. Because of the large populations covered and consequent large numbers of deaths, data can be evaluated for even rare malignancies. Similar to the previous mortality analyses through 1969, no consistent patterns with increasing duration of fluoridation were noted for any of these forms of cancer. While this analysis incorporates substantial improvements (larger numbers, control for geographic region, and removal of counties with substantial levels of natural fluoride from the comparison group) over the original study (6), the results of the two analyses are obviously not independent of one another. The major advantage is 16 additional years of mortality data, so we could evaluate longer durations of fluoridation. By comparing three time intervals from 20 to 35 years post-fluoridation to three intervals prior to fluoridation, we found more evidence of an

inverse relationship between fluoridation and cancer risk than a positive one. For seven site groupings, the O/E ratios in the three longer intervals were all below the lowest ratio for the 15 years prior to fluoridation among both males and females (all sites combined, lung, colon and rectum, pancreas and brain cancers, non-Hodgkin's lymphoma, and multiple myeloma). Inverse relationships were seen among males for esophagus, stomach, larynx and thyroid cancers, and among females for nasopharyngeal, ovarian and renal cancer and malignant melanoma. The converse, higher O/E ratios in the three longer intervals than any of those seen during the 15 years prior to fluoridation was not seen for any form of cancer.

Once again, we applied some liberal guidelines as to which cancer sites (in addition to bone and oral cancers) to single out for further scrutiny. Focusing on the three time intervals from 20 to 35 years of fluoridation, we searched for such sites where any one of these three O/E ratios surpassed the highest O/E ratio in the 15 years prior to fluoridation. This criterion was met for cancers of the lip in both sexes, for "other" cancers and for Hodgkin's disease in males only, for salivary gland, stomach, larynx and thyroid cancers in females only, and for uterine and testicular cancers. On the basis of chance alone, one would expect that 50 percent of the time the highest O/E ratio for the 20 to 35 year categories would be greater than the highest ratio for the categories 1 to 15 years prior to fluoridation. Thus, among the 46 site-sex comparisons excluding bone and oral cancers in Appendix Table G, we should have identified 23 such instances on the basis of chance alone, compared to the ten we did identify. Not only is the total number selected consistent with chance, so are the individual patterns by site. Lip cancer was the only site where our criterion was met for both sexes, was the rarest site investigated, and gave the most evidence of random variation. Among males, the highest O/E ratio was in the longest duration-of-fluoridation category, but was based on only 17 deaths, while the ratios for 15 to 29 years post fluoridation were consistent with those for the 15 years prior to fluoridation. Among females, the highest post-fluoridation O/E ratio for lip cancer was in the 20-24 year interval, while much lower ratios were seen in the 15-19 and 30-35 year intervals.

A similar lack of consistency was noted for cancer sites in which our criterion for further inspection applied to only one sex. For Hodgkin's disease among males, the O/E ratio in the 20-24 year post-fluoridation group was higher than the O/E ratios in the three groups 15 years prior to fluoridation. However, this ratio was lower than those seen 26-35 years prior to fluoridation, while the ratio for the longest post-fluoridation group was the lowest of the 14 investigated. For "other" cancers in males, the O/E ratio 30-35 years post-fluoridation was higher than the ratios in the 15 years prior to fluoridation. However, this was only marginally so, 1.11 versus 1.10 for the 11-15 years preceding fluoridation, while the ratios for 21-35 years prior to fluoridation were higher. The O/E ratio for thyroid cancer in females for the 25-29 year interval was 1.46 compared to 1.17-1.25 for the 15 years prior to fluoridation, but it decreased to 1.23 for the longest duration group. Among females with stomach cancer, the largest O/E ratio was also in the 25-29 year interval, but this was followed by a ratio that was lower than any during the fluoridated time periods, and lower than the pre-fluoridation values up to 20 years prior to fluoridation. For laryngeal cancer among women, the O/E ratio for 30-35 years post fluoridation was greater than those for the 15 years prior to fluoridation, but only marginally (1.30 vs. 1.29), and was lower than the O/E ratio within the 5 years following fluoridation. As noted above, there was evidence of an inverse relationship between the O/E ratios and fluoridation for each of these last 3 sites (thyroid, stomach, and larynx) among males.

The O/E ratio for testicular cancer was also elevated for the 25-29 year post-fluoridation period, but the value for the longest duration group was lower than the ratio for the period 21-25 years prior to fluoridation. The O/E ratio for cancer of the uterus excluding cervix in the longest post-fluoridation period (1.02) was slightly higher than that for the five-year period prior to fluoridation (0.96). However, there was no evidence of a trend, and the ratio for the 25-29 year interval was the lowest of any group following fluoridation.

Finally, it is noteworthy that none of the six cancer sites singled out for further analysis based on the incidence data showed any evidence of a positive relationship with fluoridation in the mortality

analyses. For three of these six sites (renal and colorectal cancers, and non-Hodgkin's lymphoma), there was actually evidence of an inverse relationship between duration of fluoridation and cancer mortality.

DISCUSSION

This updated survey of the risk of cancer related to artificial fluoridation of community water supplies offers several improvements over our earlier study (6). With respect to cancer mortality, several technical advances in methodology were possible and, in particular, the inclusion of 16 additional years of data enhanced the statistical power of the study and permitted us to evaluate the influence of up to 35 years of fluoridation. In addition, for the first time, an evaluation of cancer incidence could be performed with reasonable numbers of cases available for analysis. Cancers of the bones and joints, with emphasis on osteosarcomas, and cancers of the oral cavity and pharynx were evaluated in detail because of *a-priori* suspicion of a carcinogenic hazard, based on a preliminary report of the National Toxicology Program's bioassay of the effects of sodium fluoride administration in rodents (4).

For cancers of the bones and joints, there were no mortality or incidence patterns that suggested an effect of fluoridation. Analysis of over 12,000 deaths from bone and joint cancers in fluoridated counties indicated a very similar risk to that seen in non-fluoridated counties, in various periods before and after fluoridation. However, mortality data for this site are not generally of high quality, because deaths certified as bone cancer often include a substantial number of deaths due to metastatic cancers arising from other primary sites. Using population-based cancer registries in the SEER program, we were able to evaluate with greater precision the relation of water fluoridation to the incidence of bone cancer and specifically to osteosarcoma. Overall, and among males (to which the effect was restricted in rodents), there were no patterns of increasing risks of bone cancers or osteosarcomas with increasing duration of fluoridation.

The patterns of oral cancer also revealed no evidence of a fluoridation effect. Overall, mortality from oral cancer was somewhat higher in fluoridated counties than in non-fluoridated counties. However, this excess was evident in the study counties for 30 years prior to their becoming fluoridated, as well as afterwards. This negative finding is statistically stable, since it was based on over 46,000 oral cancer deaths in the fluoridated counties and 24,000 deaths in the control counties. Analysis of over 2,600 incident cases of oral cancer in fluoridated counties and 1,100 cases in control counties in two SEER registry areas also failed to reveal any patterns consistent with a fluoridation effect. An increasing trend in observed-to-expected ratios for oral cancer by increasing duration of fluoridation was seen for males in Iowa, but this pattern was not seen for males in Seattle or for females in either area.

While there was no epidemiologic evidence of a carcinogenic effect of fluoride for cancer sites under suspicion (bone and oral cavity), the availability of data on cancer of all forms allowed us to search for patterns among various cancer sites that might be associated with fluoridation status. This *a-posteriori* exploration would be expected to reveal some associations on the basis of chance alone in a certain number of instances. Therefore, our main criterion for an effect that might warrant pursuit in more analytic studies was that of consistency. When risks increased with duration of fluoridation, or were highest in the longest duration categories, the patterns were examined for consistency between the sexes, across geographic areas, and in different time periods. Even if there were a sex-specific effect, one would expect to see consistency across the other parameters. Since for most cancer sites, epidemiologic variation is similar for incidence and mortality rates, one would also expect to see similar patterns by fluoridation in both data sets. Extremely liberal criteria were used to identify sites which might be showing a fluoridation effect, so that further evaluation could be carried out for indications of consistency. The result was that no site showed any consistent evidence of a fluoridation effect.

The only hint of a possible effect was seen in the incidence data for renal cancer. There was an increasing trend in the O/E ratios by duration of fluoridation for the sexes combined in both registries. The patterns in the sex-specific data were more variable, but the highest ratio was in the longest duration-of-fluoridation category for three of the four sex-registry groups. Beyond this point, however, there was no consistency. When the 15-year incidence data were divided into two calendar-time groups, trends were not seen within the periods. In addition, the number of ratios that were highest in the longest intervals of fluoridation was consistent with the number expected on the basis of chance. Finally, evaluation of mortality data for renal cancer revealed generally lower risk in the years after fluoridation than in those immediately before, particularly for the longest durations of fluoridation.

Thus, this long-term survey of counties undergoing rapid fluoridation of community water supplies uncovered no consistent patterns of cancer incidence or mortality that suggested a relation to fluoridation. Indeed, no evidence was found to even suggest that further, more analytic epidemiologic investigation of a fluoride effect is warranted for any cancer site.

To avoid over-interpretation of these negative results, certain limitations of these analyses need discussion. While this survey deals with areas in which virtually all of the population was exposed to the agent of interest, it is still an ecologic or correlation study. That is, exposure and disease information is available for aggregate county populations, not for individuals. Thus, some subjects in both the fluoridated and non-fluoridated areas have not spent their entire lives in these areas, and may have been exposed or unexposed to fluoridated drinking water for the varying periods spent outside of these areas. There is no reason to believe that this misclassification of the exposure would be biased (i.e., different for those who developed cancer vs. those who did not), but the resulting random misclassification may tend to obscure real associations. Another potential source of random misclassification is the opportunity for exposure to fluoride from other sources (e.g., dentifrice, vitamins, foods), which might tend to restrict our ability to detect real differences associated with water treatment. However, the major source of systemic exposure to fluoride is the drinking water in areas having fluoridated water systems (17).

The method of analysis used in this study, while having many advantages, also has some potential disadvantages. Different counties at differing time periods were grouped according to their relation to the time of fluoridation. Thus, the same counties do not contribute to all of the time-to-fluoridation categories, and when counties contribute to multiple categories, their relative contribution will be different from category to category. This was done purposefully, since the aim of the analysis was to determine if any temporal patterns of risk seemed related to fluoride exposure, rather than to other underlying factors (e.g., change in the mix of populations being compared) which are assumed to act randomly with respect to time of fluoridation. It is possible, however, that if a large county or grouping of counties had an unusual cancer experience, and appeared only at one end or the other of the time-to-fluoridation groupings, then the patterns in O/E ratios could be biased. This was in fact the main reason for the registry- and time-specific incidence analyses. If a pattern in the total series represents a fluoride effect, then it should appear consistently in these subgroup analyses. However, if the pattern is an artifact of the mixture of counties being compared, then it should not appear consistently in the subcategories, since different groupings of counties are being compared. We would have done similar subgroup analyses by geographic region and calendar time for the mortality data, if any consistent or provocative patterns were seen in the aggregate data, but none were. The marked similarity of the O/E ratios by type of cancer for different time-to-fluoridation categories provided further evidence that the results were not likely to be biased.

In this survey, factors other than age, geographic area, calendar time and sex were not explicitly adjusted for in the analysis. However, the time-trend analysis should have controlled for most of these differences, since it allowed fluoridated and non-fluoridated areas to have different risks due to other factors and looked for changes in baseline differences that might relate to the timing of fluoridation. It is possible, however, that the analyses may have been influenced by time trends in other risk factors for cancer that varied between fluoridated and non-fluoridated areas. Explicit control for

socio-demographic and other potential risk factors at the county level with the Poisson regression analyses would have been the next step, if any type of cancer emerged from the main analyses with any consistent evidence of a relationship to fluoridation. But none did. We will be pursuing some of these analyses over the next several months to explore the reasons for baseline differences in cancer rates between fluoridated and non-fluoridated areas prior to fluoridation. In this process we will also be able to evaluate whether any provocative patterns were obscured by these differences.

Finally, as in any epidemiologic investigation, very small increases in risk would not be detectable by studies in human populations. If fluoridation of water supplies is associated with a few extra cases of bone cancer in tens of millions of people, then no methodology would be able to detect this and attribute a causal interpretation to the difference. Even explorations of the 10% to 20% differences in ratios that took place in this analysis must be considered at the limits of what could be detected relative to the background forces of incidence and mortality for these tumors.

With all of these caveats in mind, however, it should be pointed out that while this was an ecologic study, it was a strong ecologic study. Many such investigations look for differences in risk related to differences in average values for social class-related or other variables where there is considerable overlap between the populations being compared. Others investigate the influence of exposures that apply to only a small minority of the populations investigated (e.g., occupations). The current investigation was able to evaluate the influence of an abrupt switch from non-fluoridated to fluoridated drinking water on the part of the vast majority of the populations under study. Ecologic studies of general environmental exposures that were much more crudely measured (18), or applied to much smaller segments of the population (19), have generated evidence of associations, which have been confirmed as low-level hazards by subsequent analytic investigations (20-21). Thus, the failure to detect any evidence of a consistent relationship between water fluoridation and cancer risk, either for cancer types suggested by the rodent studies or for any other forms of cancer, should be reassuring. The findings should also help put into perspective what the maximum magnitude of any potential risk might be.

SUMMARY

In response to concerns over the possible carcinogenicity of fluoride compounds added to drinking water raised by the results of a recent animal experiment, we evaluated 36 years of U.S. cancer mortality data and 15 years of cancer incidence data from two population-based cancer registries, in relation to the fluoridation status of drinking water supplies in the populations under study. Osteosarcomas of the bone were singled out for detailed analysis based on the results of the animal experiment. Among both males and females residing in counties having undergone rapid fluoridation, the relative risk of death from cancers of the bones and joints was the same after 20-35 years of fluoridation as it was in the years immediately preceding fluoridation. A similar lack of a relationship to timing of fluoridation was noted for the incidence of bone and joint cancers, and osteosarcomas. The relative risk of developing these cancers 20 or more years after fluoridation was lower than the risk associated with less than five years of fluoridation among both males and females.

The mortality and incidence data in this survey allowed an evaluation of the patterns of risk for virtually all forms of cancer in relation to the timing of fluoridation of drinking water supplies. For no type of malignancy was there consistent evidence of a relationship with the patterns of fluoridation. One site, renal cancer, showed a suggestive relationship between incidence rates and duration of fluoridation in the aggregate data from the registries. However, no such trends were seen when incidence data were examined for two separate periods, and the mortality data for renal cancer actually yielded some evidence of an inverse relationship with duration of fluoridation.

Thus, in a study of over 2,300,000 cancer deaths in fluoridated counties across the United States, and over 125,000 incident cancer cases in fluoridated counties covered by two population-based cancer registries, we identified no trends in cancer risk that could be ascribed to the consumption of fluoridated drinking water.

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APPENDIX TABLE E. List of counties used in the mortality analysis

	Year Started Fluoridation[a]	County Name
Region=West:	1947	Nez Perce, ID
	1952	San Francisco, CA
	1954	Denver, CO
	1954	Hot Springs, WY
	1955	Custer, MT
	1956	Colfax, NM
	1966	Albany, WY
	1968	Los Alamos, NM
	1970	King, WA
	1974	Bernalillo, NM
	1974	Laramie, WY
	1982	Pueblo, CO
	-NF-	Coconino, AZ
	-NF-	Pima, AZ
	-NF-	Fresno, CA
	-NF-	Imperial, CA
	-NF-	Kern, CA
	-NF-	Kings, CA
	-NF-	Monterey, CA
	-NF-	Napa, CA
	-NF-	Riverside, CA
	-NF-	Sacramento, CA
	-NF-	San Bernardino, CA
	-NF-	San Diego, CA
	-NF-	San Joaquin, CA
	-NF-	Santa Barbara, CA
	-NF-	Santa Cruz, CA
	-NF-	Shasta, CA
	-NF-	Sonoma, CA
	-NF-	Stanislaus, CA
	-NF-	Sutter, CA
	-NF-	Tulare, CA
	-NF-	Ventura, CA
	-NF-	Yolo, CA
	-NF-	Yuba, CA
	-NF-	Gunnison, CO
	-NF-	Logan, CO
	-NF-	Bannock, ID
	-NF-	Bonneville, ID
	-NF-	Power, ID
	-NF-	Washington, ID
	-NF-	Deer Lodge, MT
	-NF-	Fergus, MT
	-NF-	Hill, MT
	-NF-	Lewis and Clark, MT

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

Year Started Fluoridation[a]	County Name
-NF-	Missoula, MT
-NF-	Park, MT
-NF-	Powell, MT
-NF-	Silver Bow, MT
-NF-	Toole, MT
-NF-	Yellowstone, MT
-NF-	Clark, NV
-NF-	Lander, NV
-NF-	Mineral, NV
-NF-	Ormsby, NV
-NF-	Washoe, NV
-NF-	White Pine, NV
-NF-	Dona Ana, NM
-NF-	Baker, OR
-NF-	Clackamas, OR
-NF-	Jackson, OR
-NF-	Klamath, OR
-NF-	Lane, OR
-NF-	Multnomah, OR
-NF-	Cache, UT
-NF-	Davis, UT
-NF-	Grand, UT
-NF-	Iron, UT
-NF-	Juab, UT
-NF-	Salt Lake, UT
-NF-	Tooele, UT
-NF-	Utah, UT
-NF-	Wasatch, UT
-NF-	Washington, UT
-NF-	Weber, UT
-NF-	Benton, WA
-NF-	Columbia, WA
-NF-	Douglas, WA
-NF-	Franklin, WA
-NF-	Grays Harbor, WA
-NF-	Pierce, WA
-NF-	Spokane, WA
-NF-	Thurston, WA
-NF-	Walla Walla, WA
-NF-	Whatcom, WA
-NF-	Converse, WY
-NF-	Johnson, WY
-NF-	Natrona, WY
-NF-	Sheridan, WY
-NF-	Sweetwater, WY

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

	Year Started Fluoridation[a]	County Name
	-NF-	Washakie, WY
Region = North Central:	1949	Rock, WI
	1951	Marion, ID
	1951	Brown, SD
	1951	Clay, SD
	1952	Scott, IA
	1952	Cass, ND
	1952	Stark, ND
	1953	Douglas, KS
	1953	Codington, SD
	1953	Milwaukee, WI
	1954	Davison, SD
	1955	Cape Girardeau, MO
	1955	Marion, MO
	1955	St. Louis City, MO
	1955	Burleigh, ND
	1955	Lucas, OH
	1956	Cook, IL
	1956	Morgan, IL
	1956	Stutsman, ND
	1956	Cuyahoga, OH
	1956	Beadle, SD
	1957	Shawnee, KS
	1958	Wapello, IA
	1958	Grand Forks, ND
	1959	Lyon, KS
	1962	Pottawattamie, IA
	1962	Ramsey, MN
	1963	Vanderburgh, IN
	1963	St. Louis, MO
	1964	Wyandotte, KS
	1964	Eau Claire, WI
	1965	Clay, MN
	1967	Wayne, MI
	1967	Nicollet, MN
	1968	Logan, IL
	1968	Macon, IL
	1968	Douglas, NE
	1968	Hughes, SD
	1969	Wabash, IL
	1969	Summit, OH
	1969	Champaign, IL
	1969	Saline, KS

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

	Year Started Fluoridation[a]	County Name
	1970	Minnehaha, SD
	1973	Woodbury, IA
	1973	Franklin, OH
	1974	Adair, MO
	1983	Greene, MO
	-NF-	Fayette, IN
	-NF-	Vigo, IN
	-NF-	Clay, KS
	-NF-	Cloud, KS
	-NF-	Harvey, KS
	-NF-	McPherson, KS
	-NF-	Mitchell, KS
	-NF-	Norton, KS
	-NF-	Pratt, KS
	-NF-	Reno, KS
	-NF-	Russell, KS
	-NF-	Sedgwick, KS
	-NF-	Seward, KS
	-NF-	Stevens, KS
	-NF-	Dickinson, MI
	-NF-	Buchanan, MO
	-NF-	Adams, NE
	-NF-	Dakota, NE
	-NF-	Dawson, NE
	-NF-	Dodge, NE
	-NF-	Gage, NE
	-NF-	Hall, NE
	-NF-	Kimball, NE
	-NF-	Lincoln, NE
	-NF-	Madison, NE
	-NF-	Phelps, NE
	-NF-	Red Willow, NE
	-NF-	Scott Bluff, NE
	-NF-	York, NE
	-NF-	La Crosse, WI
Region=South	1949	Mecklenburg, NC
	1950	Ohio, WV
	1951	Tuscaloosa, AL
	1951	Pulaski, AR
	1951	Clarke, GA
	1951	Jefferson, KY
	1951	Montgomery, MD
	1951	Prince Georges, MD
	1951	Brooke, WV

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

Year Started Fluoridation[a]	County Name
1952	Washington, D.C.
1952	Boyd, KY
1952	Baltimore City, MD
1952	Lamar, TX
1953	Ouachita, AR
1953	Dougherty, GA
1953	Daviess, KY
1953	Nueces, TX
1953	Cabell, WV
1954	De Kalb, GA
1954	Fayette, KY
1954	Kanawha, WV
1957	Franklin, KY
1959	Houston, AL
1959	Madison, AL
1960	Maury, TN
1960	Montgomery, TN
1961	Bradley, AR
1962	Cobb, GA
1962	Henderson, KY
1962	Durham, NC
1962	Madison, TN
1963	Gwinnett, GA
1964	Simpson, KY
1965	Tarrant, TX
1966	Mc Cracken, KY
1966	Dallas, TX
1967	Garfield, OK
1967	Richland, SC
1967	Hopkins, TX
1968	Warren, KY
1969	Jefferson, AR
1969	Fulton, GA
1969	Hinds, MS
1970	Shelby, TN
1971	Comanche, OK
1972	Travis, TX
1973	Greenville, SC
1974	Chatham, GA
1974	Muscogee, GA
1974	Orleans, LA
1976	Forrest, MS
1979	Montgomery, AL
1980	Caddo, LA
1981	Autauga, AL

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

Year Started Fluoridation[a]	County Name
1981	Jefferson, AL
1981	Bossier, LA
1982	Bibb, GA
1982	Harris, TX
1982	Zavala, TX
1983	Jefferson, AL
1983	St. John the Baptist, LA
1983	Jackson, OK
1983	Calhoun, TX
1983	Comal, TX
1985	Victoria, TX
-NF-	Garland, AR
-NF-	Miller, AR
-NF-	Sebastian, AR
-NF-	Union, AR
-NF-	Bay, FL
-NF-	Charlotte, FL
-NF-	Clay, FL
-NF-	Escambia, FL
-NF-	Hillsborough, FL
-NF-	Leon, FL
-NF-	Martin, FL
-NF-	Palm Beach, FL
-NF-	Pasco, FL
-NF-	Pinellas, FL
-NF-	Chattahoochee, GA
-NF-	Acadia, LA
-NF-	Iberia, LA
-NF-	Lafayette, LA
-NF-	Lincoln, LA
-NF-	Madison, LA
-NF-	Ouachita, LA
-NF-	Plaquemines, LA
-NF-	St. Bernard, LA
-NF-	Allegany, MD
-NF-	Coahoma, MS
-NF-	Grenada, MS
-NF-	Leflore, MS
-NF-	Canadian, OK
-NF-	Okmulgee, OK
-NF-	Woodward, OK
-NF-	Bailey, TX
-NF-	Bexar, TX
-NF-	Bowie, TX
-NF-	Cameron, TX

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

	Year Started Fluoridation[a]	County Name
	-NF-	Coleman, TX
	-NF-	Collingsworth, TX
	-NF-	Crane, TX
	-NF-	Dimmit, TX
	-NF-	Eastland, TX
	-NF-	Erath, TX
	-NF-	Fort Bend, TX
	-NF-	Frio, TX
	-NF-	Hardeman, TX
	-NF-	Hartley, TX
	-NF-	Howard, TX
	-NF-	Kimble, TX
	-NF-	Kleberg, TX
	-NF-	Lampasas, TX
	-NF-	La Salle, TX
	-NF-	Limestone, TX
	-NF-	Palo Pinto, TX
	-NF-	Scurry, TX
	-NF-	Sutton, TX
	-NF-	Taylor, TX
	-NF-	Titus, TX
	-NF-	Tom Green, TX
	-NF-	Uvalde, TX
	-NF-	Young, TX
	-NF-	Brown, TX
Region=North-East:	1952	Bristol, RI
	1954	Philadelphia, PA
	1964	Mercer, NJ
	1965	New York, NY
	1967	New Haven, CT
	1970	Androscoggin, ME
	1978	Suffolk, MA
	-NF-	Berkshire, MA
	-NF-	Hampden, MA
	-NF-	Hampshire, MA
	-NF-	Nantucket, MA
	-NF-	Hillsborough, NH
	-NF-	Sullivan, NH
	-NF-	Bergen, NJ
	-NF-	Camden, NJ
	-NF-	Cape May, NJ
	-NF-	Cumberland, NJ
	-NF-	Essex, NJ
	-NF-	Hudson, NJ

[a] "NF" = Not Fluoridated

APPENDIX TABLE E. List of counties used in the mortality analysis (cont.)

Year Started Fluoridation[a]	County Name
-NF-	Morris, NJ
-NF-	Ocean, NJ
-NF-	Passaic, NJ
-NF-	Salem, NJ
-NF-	Union, NJ
-NF-	Albany, NY
-NF-	Blair, PA
-NF-	Cambria, PA
-NF-	Delaware, PA
-NF-	Erie, PA
-NF-	Lackawanna, PA
-NF-	Lehigh, PA
-NF-	Luzerne, PA
-NF-	Montgomery, PA
-NF-	Washington, PA

[a] "NF" = Not Fluoridated

APPENDIX TABLE F. Definition of Cancer Sites Used in the Mortality Analysis

Site	6th, 7th[a]	8th[a]	9th[a]
Lip	140	140	140
Salivary Glands	142	142	142
Other Oral	141, 143-5 147-8	141,143-6, 148-9	141, 143-6, 148-9
Nasapharynx	146	147	147
Esophagus	150	150	150
Stomach	151	151	151
Colon and Rectum	153, 154	153, 154	153, 154 ex. 154.3, 159.0
Liver	155	155, 156	155, 156 ex. 155.2
Pancreas	157	157	157
Larynx	161	161	161
Lung (inc. bronchus and pleura)	162, 163	162, 163.0	162, 163
Bones and joints	196	170	170
Soft tissue	197	171	171
Melanoma of the skin	190	172	172
Breast	170	174	174
Cervix uteri	171	180	180
Corpus uteri and uterus NOS	172-4	181-182	179, 181, 182
Ovary	175	183	183
Prostate gland	177	185	185
Testis	178	186	186
Bladder	181	188, 189.9	188, 189.3-9
Kidney (inc. renal and ureter)	180	189.0-2	189.0-2
Brain and nervous system	193	191, 192	191, 192
Thyroid	194	193	193
Hodgkin's disease	201	201	201
Non-Hodgkin's lymphomas	200, 202, 205	200, 202	159.1, 200, 202 ex. 202.2-.6
Multiple myeloma	203	203	203 ex. 203.1
Leukemias	204	204-207	202.4, 203.1 204-208 ex 207.1
Other cancers	152, 156, 158-160, 164, 165, 176, 179, 191, 192 195, 198, 199	152, 158-160, 163.1-9, 173, 184, 187, 190, 194-198	152, 154.3, 155.2, 158, 159.2-160.9, 164, 165, 173, 184, 187, 190, 194-198
All cancer sites	140-205	140-207	140-208 ex. 202.2, 202.3, 202.5, 202.6, 207.1

[a] Sources: (23-26).

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

Time rel. to start of fluor.	All Cancer Sites				Lip				Salivary Glands			
	Males		Females		Males		Females		Males		Females	
	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.07	1604	1.05	1593	0.71	4	1.15	3	3.31	9	1.08	3
30-26 PRE	1.12	8114	1.04	7352	0.81	16	2.46	3	1.08	25	1.28	14
25-21 PRE	1.14	15303	1.05	13663	1.14	40	1.14	6	1.32	41	1.18	28
20-16 PRE	1.13	31988	1.07	28813	0.99	85	0.50	6	0.98	79	0.95	59
15-11 PRE	1.14	88560	1.10	79784	0.66	137	0.86	17	0.79	188	1.03	131
10-6 PRE	1.12	104354	1.09	91725	0.81	136	0.83	11	0.94	242	0.99	144
5-1 PRE	1.12	149807	1.06	133040	0.56	171	0.30	15	0.97	336	0.77	183
0-4 POST	1.09	169656	1.07	151525	0.72	178	1.27	29	0.90	409	1.16	263
5-9 POST	1.07	161113	1.05	144945	0.84	137	0.79	13	0.97	354	1.08	226
10-14 POST	1.04	156744	1.03	142537	0.67	110	0.80	14	0.89	315	0.96	223
15-19 POST	1.01	137693	1.02	127267	0.89	82	0.40	9	0.90	252	1.07	192
20-24 POST	1.01	87436	1.03	79870	0.68	54	1.65	12	0.76	163	0.84	105
25-29 POST	1.03	73510	1.03	67844	0.58	31	1.41	12	0.94	112	1.04	98
30-35 POST	1.05	31557	1.04	29655	1.50	17	0.82	4	0.91	43	1.01	36

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Nasopharynx				Esophagus				Stomach			
	Males		Females		Males		Females		Males		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.19	8	0.00	0	0.91	28	1.47	15	0.98	179	0.92	105
30-26 PRE	1.40	26	1.20	7	1.41	254	1.47	74	0.99	800	1.02	529
25-21 PRE	1.31	50	1.06	15	1.38	448	1.20	121	1.02	1343	0.99	892
20-16 PRE	1.47	106	1.02	25	1.35	842	1.33	272	1.10	2982	1.08	1922
15-11 PRE	1.24	211	1.31	75	1.28	2622	1.49	768	1.16	9372	1.13	5806
10-6 PRE	1.28	230	1.24	82	1.29	2934	1.33	894	1.16	9404	1.17	5979
5-1 PRE	1.18	327	1.32	114	1.49	4597	1.21	1223	1.18	12954	1.14	8224
0-4 POST	1.14	285	1.17	105	1.39	4718	1.21	1424	1.13	12226	1.18	8193
5-9 POST	1.14	193	0.87	66	1.34	4433	1.23	1478	1.17	10294	1.16	6857
10-14 POST	1.27	211	1.23	89	1.22	3974	1.21	1520	1.14	8206	1.15	5876
15-19 POST	1.09	143	0.93	66	1.23	3522	1.14	1326	1.13	6278	1.15	4564
20-24 POST	1.18	59	0.83	23	1.26	2236	1.32	848	1.14	3763	1.18	2716
25-29 POST	1.13	116	0.86	69	1.25	1835	1.06	663	1.15	2822	1.25	2018
30-35 POST	0.99	55	1.03	32	1.13	738	1.10	325	0.98	968	1.02	735

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

Time rel. to start of fluor.	Colon and Rectum				Liver				Pancreas			
	Males		Females		Males		Females		Males		Females	
	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	0.80	146	1.08	219	2.12	40	1.57	50	1.04	95	1.34	67
30-26 PRE	0.97	942	1.06	1138	1.59	181	1.23	199	1.09	431	1.12	307
25-21 PRE	1.06	1932	1.05	2182	1.27	99	1.05	358	1.17	856	1.10	614
20-16 PRE	1.14	4203	1.09	4533	1.25	591	1.00	724	1.09	1754	1.08	1254
15-11 PRE	1.18	13591	1.12	13735	1.17	1501	1.11	2191	1.13	4748	1.18	3427
10-6 PRE	1.18	15641	1.08	15361	1.24	1877	1.08	2540	1.12	5780	1.12	4286
5-1 PRE	1.19	22262	1.08	22293	1.30	2908	1.03	3668	1.10	8180	1.12	6357
0-4 POST	1.19	24917	1.09	24873	1.16	3055	1.04	4124	1.09	9370	1.10	7497
5-9 POST	1.16	23129	1.06	24047	1.17	3010	1.01	3778	1.07	9053	1.08	7523
10-14 POST	1.09	21726	1.02	22672	1.18	3054	1.00	3627	1.05	8622	1.06	7538
15-19 POST	1.07	18829	1.01	19734	1.20	2852	1.02	3227	1.00	7268	1.04	6961
20-24 POST	1.11	11656	1.02	12216	1.20	1741	1.02	1913	0.97	4519	1.02	4274
25-29 POST	1.07	9578	1.04	10024	1.27	1671	1.04	1814	1.03	3625	1.01	3840
30-35 POST	1.08	3872	1.03	4125	1.10	700	0.95	708	1.05	1507	0.97	1564

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Larynx				Lung				Soft Tissue			
	Males		Females		Males		Females		Males		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.12	24	0.67	2	1.25	322	0.92	58	0.93	5	0.67	4
30-26 PRE	1.34	165	1.19	16	1.24	1684	1.11	288	1.91	32	0.92	21
25-21 PRE	1.45	298	0.72	17	1.25	3570	1.16	634	1.13	56	1.23	53
20-16 PRE	1.28	550	1.07	54	1.21	7359	1.07	1300	1.00	117	1.10	95
15-11 PRE	1.37	1696	1.09	134	1.21	19807	1.20	3764	0.97	299	1.40	282
10-6 PRE	1.29	1830	1.29	202	1.16	26196	1.22	5494	1.10	406	1.07	299
5-1 PRE	1.37	2660	1.27	285	1.15	38185	1.15	8657	0.90	581	1.21	513
0-4 POST	1.24	2799	1.33	355	1.11	46200	1.14	11619	0.96	707	1.09	614
5-9 POST	1.32	2685	1.13	348	1.06	46541	1.16	12878	0.98	662	1.12	673
10-14 POST	1.21	2540	1.19	413	1.03	48266	1.09	15604	1.00	739	0.94	670
15-19 POST	1.19	2122	1.21	387	0.99	43905	1.08	16466	0.96	671	0.96	672
20-24 POST	1.20	1336	1.01	251	1.00	28885	1.08	10793	0.95	367	0.87	387
25-29 POST	1.14	1071	1.18	236	1.01	24966	1.09	10725	1.04	397	0.90	407
30-35 POST	1.10	378	1.30	104	1.05	11219	1.07	5450	1.05	182	1.09	211

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Melanoma of the Skin				Breast		Cervix Uteri	
	Males		Females		Females		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.03	18	1.38	17	0.94	240	1.16	1.74
30-26 PRE	1.54	113	1.05	70	1.06	1363	1.08	614
25-21 PRE	1.00	155	1.04	119	1.08	2573	1.02	1035
20-16 PRE	1.11	343	1.16	268	1.10	5599	1.10	2209
15-11 PRE	1.03	749	1.03	577	1.13	16063	1.02	4773
10-6 PRE	0.97	898	1.05	753	1.10	18599	0.94	4631
5-1 PRE	0.92	1328	0.98	1032	1.08	27029	0.87	6201
0-4 POST	1.01	1711	0.95	1308	1.10	30974	0.89	6543
5-9 POST	0.92	1663	0.95	1302	1.07	30044	0.86	5496
10-14 POST	0.95	1809	0.93	1345	1.07	29357	0.84	4567
15-19 POST	0.96	1686	0.88	1255	1.04	25991	0.82	3284
20-24 POST	0.90	1061	0.86	759	1.04	16219	0.83	1935
25-29 POST	0.90	895	0.81	674	1.05	13375	0.83	1355
30-35 POST	0.93	434	0.89	329	1.08	5783	0.97	542

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

Time rel. to start of fluor.	Uterus (Corpus and NOS) Females		Ovary Females		Prostate Males	
	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	0.92	107	0.97	78	0.96	141
30-26 PRE	0.73	344	1.11	455	1.12	767
25-21 PRE	0.92	689	1.04	847	1.07	1362
20-16 PRE	0.88	1340	1.01	1786	1.09	2948
15-11 PRE	0.82	3387	1.05	5070	1.02	7009
10-6 PRE	0.94	3807	1.05	6030	0.98	8375
5-1 PRE	0.96	5840	1.02	8778	0.98	12240
0-4 POST	0.96	5958	1.03	10162	0.97	14236
5-9 POST	0.99	5336	0.99	9588	0.94	13795
10-14 POST	1.01	4996	0.99	9311	0.94	13926
15-19 POST	0.96	4026	0.99	8039	0.92	12512
20-24 POST	0.99	2474	0.98	5187	0.90	7708
25-29 POST	0.94	1992	0.97	4033	0.93	6905
30-35 POST	1.02	815	1.01	1639	0.98	2982

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Brain and Nervous System				Thyroid				Hodgkin's Disease			
	Males		Females		Males		Females		Males		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	0.90	43	1.40	31	1.19	5	1.76	10	1.42	31	0.92	16
30-26 PRE	1.18	242	1.16	167	1.16	27	0.82	29	1.15	147	1.12	88
25-21 PRE	1.16	466	1.12	304	0.73	29	1.07	68	1.07	234	1.12	153
20-16 PRE	1.14	975	1.17	662	0.93	73	1.00	130	1.05	512	1.06	307
15-11 PRE	1.16	2491	1.21	1743	1.17	272	1.25	458	1.07	1328	1.17	843
10-6 PRE	1.14	2918	1.12	2034	1.15	288	1.17	519	1.02	1367	1.14	984
5-1 PRE	1.06	3941	1.09	2923	1.18	411	1.17	714	0.99	1907	1.13	1291
0-4 POST	1.06	4578	1.02	3314	1.19	440	1.26	805	0.97	2004	1.01	1368
5-9 POST	1.02	4231	1.03	3276	1.01	353	1.04	677	0.99	1692	1.07	1235
10-14 POST	0.99	4055	.94	3194	1.00	317	0.98	557	0.93	1376	1.01	1038
15-19 POST	0.90	3378	0.94	2813	0.97	250	1.17	481	1.00	1139	1.10	905
20-24 POST	0.90	2251	0.94	1866	1.04	148	1.07	295	1.09	636	0.97	430
25-29 POST	0.90	1803	0.96	1512	0.79	113	1.46	227	1.07	413	1.15	319
30-35 POST	0.95	749	0.98	657	0.83	47	1.23	89	0.83	134	1.01	109

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

Time rel. to start of fluor.	Testis Males		Bladder Males		Bladder Females		Kidney Males		Kidney Females	
	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.04	8	1.07	63	0.92	26	0.83	28	1.35	32
30-26 PRE	1.00	45	1.06	317	0.89	123	1.05	178	1.02	106
25-21 PRE	1.06	88	0.98	520	0.99	249	1.08	340	0.94	189
20-16 PRE	0.99	185	1.13	1230	1.08	536	1.11	717	0.98	403
15-11 PRE	0.97	434	1.08	3488	1.09	1479	1.13	2077	1.08	1153
10-6 PRE	0.87	445	1.07	3954	1.09	1713	1.10	2360	1.08	1434
5-1 PRE	0.81	610	1.12	5873	1.13	2475	1.02	3286	0.98	2028
0-4 POST	0.99	760	1.09	6430	1.08	2789	1.06	3976	0.96	2306
5-9 POST	0.95	680	1.08	6121	1.10	2629	1.06	3844	0.92	2192
10-14 POST	0.93	582	1.06	5675	1.11	2619	1.03	3697	0.95	2221
15-19 POST	0.79	416	1.03	4831	1.00	2173	0.96	3173	0.88	1995
20-24 POST	0.83	285	1.05	3029	1.09	1402	1.02	2083	0.92	1283
25-29 POST	1.11	175	1.06	2405	1.01	1073	1.03	1694	0.85	1106
30-35 POST	1.03	67	1.08	960	1.05	484	1.02	721	0.95	485

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Non-Hodgkin's Lymphoma				Multiple Myeloma				Leukemias			
	Males		Females		Males		Females		Males		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.28	43	2.06	44	0.93	12	1.49	13	1.26	107	0.93	61
30-26 PRE	1.12	215	1.16	144	1.27	80	0.84	40	1.05	413	1.01	309
25-21 PRE	1.17	443	1.13	296	1.30	160	1.05	104	1.09	797	1.00	565
20-16 PRE	1.11	908	1.33	740	1.22	302	1.21	272	1.07	1673	1.07	1258
15-11 PRE	1.11	2405	1.23	1820	1.19	810	1.20	641	1.08	4180	1.08	3242
10-6 PRE	1.12	2964	1.22	2376	1.20	1093	1.04	893	1.03	4904	1.11	3876
5-1 PRE	1.08	4248	1.14	3480	1.17	1500	1.05	1327	1.01	6888	0.99	5250
0-4 POST	1.10	5127	1.14	4282	0.97	1705	1.04	1725	0.95	7664	1.03	6209
5-9 POST	1.06	4833	1.10	4352	0.99	1898	0.92	1703	0.96	7191	0.98	5650
10-14 POST	1.03	4833	1.07	4571	0.97	1914	1.01	1898	0.98	7006	1.01	5608
15-19 POST	1.02	4360	1.04	4294	0.96	1796	0.93	1766	0.96	5971	0.97	4877
20-24 POST	1.00	2666	0.98	2573	0.85	1118	0.95	1196	0.92	3620	0.99	3035
25-29 POST	0.99	2215	1.01	2324	0.85	956	0.87	989	1.02	3078	0.99	2588
30-35 POST	1.06	1048	1.08	1069	0.97	451	0.97	483	0.95	1212	0.96	1085

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.

APPENDIX TABLE G. Observed over Expected mortality ratios[a] and number of observed deaths in rapidly fluoridated counties by years before (PRE) and after (POST) fluoridation by site of cancer, 1950-85.

	Other Cancer Sites			
	Males		Females	
Time rel. to start of fluor.	O/E Ratio	Obs. Deaths	O/E Ratio	Obs. Deaths
35-31 PRE	1.19	232	0.95	207
30-26 PRE	1.12	922	0.98	846
25-21 PRE	1.12	1559	1.03	1476
20-16 PRE	1.06	3097	0.98	2872
15-11 PRE	1.10	7897	1.07	7526
10-6 PRE	1.04	8328	1.02	7754
5-1 PRE	1.03	11533	0.99	11213
0-4 POST	1.01	11669	1.01	11417
5-9 POST	1.01	9304	0.97	9421
10-14 POST	1.02	8196	1.06	8382
15-19 POST	0.99	5425	1.00	5636
20-24 POST	1.00	3359	1.00	3493
25-29 POST	1.01	2189	0.99	2279
30-35 POST	1.11	943	0.96	859

[a]Relative to non-fluoridated counties (1.00), adjusted for age, calendar time period, and region.