APPENDIX F

TIME TRENDS FOR BONE AND JOINT CANCERS AND OSTEOSARCOMAS IN THE SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS (SEER) PROGRAM NATIONAL CANCER INSTITUTE

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At the request of the Committee, we have enclosed a brief description of the time trends for bone and joint cancers and for osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI), and the relationship of these trends to fluoridation of drinking water supplies. The SEER Program, begun in 1973, is a group of population-based cancer registries that covers approximately 10% of the U.S. population. In contrast to our main report which focused on observed/expected events, in this report we also present age-adjusted rates. As cancer rates generally increase with age, to properly compare rates among populations which may differ in age distribution, a statistical procedure called age adjustment applies a standard set of weights to age-specific rates to derive age-adjusted rates; this allows meaningful comparison while minimizing potential confounding. Table 1 presents the data for the entire SEER program split into 2 time periods (1973-80 and 1981-87). The incidence of all bone and joint cancers over all ages increased slightly between these two time periods. When examined by age, the only increase occurred for the rates among those under age 20, where an 18% rise occurred for the sexes combined, reflecting a 23% rise in males and a 13% rise in females. When osteosarcomas are considered separately, there was essentially no change in the incidence rate over time for the sexes combined, reflecting the averaging of an 18% rise for males and an 11% decline among females. Among males, the upward trend resulted mainly from the experience of those under age 20, whose rates rose from 0.36 to 0.55 (53%).

It was possible to evaluate these same trends for groupings of counties within the SEER areas that were "non-fluoridated" as well as for those undergoing abrupt fluoridation at some time before the establishment of the SEER program. The definitions of "non-fluoridated" and "fluoridated" counties were similar to those used in our previously submitted study. It should be noted that a substantial number of counties within the SEER program do not fit under either definition and thus are not informative with respect to a time-trend analysis of fluoridation. Tables 2, 3, and 4 present rates for these groupings of counties which do meet the inclusion criteria. As shown in Table 2, the pattern for the entire SEER program of a rising rate of bone and joint cancers at all ages combined, due mainly to trends under age 20, was seen in the "fluoridated" counties but not in the "non-fluoridated" counties. Tables 3 and 4 are restricted to the patterns among males. Once again, the larger increase in males under age 20 seen in the aggregate data for all bone and joint cancers is seen only in the "fluoridated" counties (Table 3). For osteosarcomas among males, increases were seen for those under age 20 in both the "fluoridated" and "non-fluoridated" areas, although more prominently in the "fluoridated" counties (Table 4).

Based on these data, one could conclude that summarized over all ages and both sexes, there were no meaningful time trends in incidence of these tumors. However, for bone and joint cancers, temporal increases were seen among those under age 20 in both sexes. For osteosarcomas, there were some increases, but only among young males. In addition, these patterns were associated with the fluoridation status of the counties for which these trends were assessed.

To determine whether these incidence trends are associated with fluoridation of water supplies, or with some other correlate of fluoridated counties, one needs to assess the relationship of risk of these tumors to fluoridation while controlling for calendar-time. This analysis was carried out in our earlier report covering the Iowa and Seattle registries. In brief, after control for age, area and calendar-time, there was no evidence of an increased risk of these tumors with increasing duration of fluoridation. For example, the observed-to-expected ratios for osteosarcomas among those under age 30 who had "lifetime" exposure to fluoridated drinking water was 0.9, compared to a value of 0.9 for those who had less than one- half of their lifetime spent in areas with fluoridated water. The expected values for both of these ratios were based on the age, sex, time and area-specific rates in non-fluoridated areas.

Our analyses utilizing all available data for the Iowa and Seattle registries did not reveal positive correlations, which should have appeared if an association existed between fluoridation and risk of bone cancers. However, since the evaluation of temporal patterns in the SEER data noted some age

and sex-specific increases, we reanalyzed our study to further investigate these subgroups. First of all, the age and sex-specific time trends and their relation to the fluoridation status of the counties covered by the Iowa and Seattle registries are similar to those described for the total SEER program. When restricted to persons under age 20, the rates for bone and joint cancers in both sexes rose 47% from 1973-80 to 1981-87 in the fluoridated areas of Seattle and Iowa and declined 34% in the non-fluoridated areas. For osteosarcomas in males under 20, the rates increased 79% in the fluoridated areas and decreased 4% in the non-fluoridated areas. With this background, Table 5 presents for the Iowa and Seattle registries, the relationship of duration of fluoridation to the risk of bone and joint cancers and osteosarcomas for those under age 20. As seen when data for all ages were analyzed in our submitted report, there was no evidence of an increase in the incidence ratios with increasing duration of fluoridation. Indeed, the ratios for osteosarcomas are lowest in the longest duration categories. Similarly, when incidence ratios were calculated for those under age 20 with "lifetime" exposure to fluoridation versus those exposed less than one-half of their life, there was no evidence of a significant positive relationship. The ratios for bone and joint cancer for both sexes were 1.3 for "lifetime" exposure and 1.2 for <1/2 "lifetime" exposure. The corresponding ratios for osteosarcomas were 1.1 and 1.5 for both sexes, and 0.6 and 1.3 for males. While the observed numbers on which some of these incidence ratios are based are relatively small, they are the same numbers which yielded the time-trend patterns. Thus, the differences in time trends between fluoridated and non-fluoridated areas for those under age 20 in these two registries is not related to the timing of fluoridation.

While we believe our analysis is the appropriate way of assessing this relationship, the conclusions revealed are supported by another methodologic approach presented in Tables 2, 3, and 4, using data for the entire Seer program. For this analysis we considered two subgroups of the "fluoridated" counties, those fluoridated early (before 1955) and those fluoridated late (after 1965). The time trends of most concern, those under age 20, are all greater for the counties fluoridated in the earlier time-period. For this group, you would expect to see no influence of fluoridation, since essentially all persons under age 20 in both time periods from these early-fluoridated counties would have been exposed for their entire life-times. Other inconsistencies with a fluoridation effect are also present. This includes a marked decline in osteosarcoma rates in males aged 20-39 between these two time-periods for the early-fluoridation countries, although one might anticipate that this age group would experience a marked impact of fluoridation if there was one.

One can quantify the relationship between interval from fluoridation of drinking water and risk of bone malignancies by analyzing all of the fluoridated and non-fluoridated counties in the SEER Program summarized in Tables 2-4 in the same manner as the Iowa and Seattle counties were analyzed. The difficulty with this approach, as noted in our earlier report, is that Iowa and Seattle were the only areas with enough of both fluoridated and non-fluoridated areas by our definitions to allow an analysis which controlled for geographic area. Thus, the expanded analysis involves adding data to the non-fluoridated areas mainly from Utah and New Mexico, and adding to the fluoridated areas data from Detroit, Atlanta, San Francisco and Connecticut. The resulting comparison of trends between these different areas could be suspect. However, since this is the comparison yielding the time-trend differences noted in the SEER program, it is useful to see if the patterns observed are indeed explained by the timing of fluoridation in these areas. Table 6 presents observed-to- expected incidence ratios by time since fluoridation (duration of fluoridation) for those under age 20 in the "fluoridated" and "non-fluoridated" counties in the entire SEER program. For none of the categories revealing differences in time trends between fluoridated and non-fluoridated areas is there any evidence of an increase in incidence ratios by duration of fluoridation. For osteosarcomas, there is even some evidence of a decline in the ratio with duration of fluoridation.

In summary, analysis of incidence data from the SEER program has revealed some age- and sex-specific increases over time for bone and joint cancers, and for osteosarcomas, which are more prominent in fluoridated than in non-fluoridated areas. However, on further analysis these increases are unrelated to the timing of fluoridation, and thus are not linked to the fluoridation of water supplies.

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TABLE 1

Average annual age-adjusted incidence rates[a] (# of cases) for bone and joint cancers and osteosarcomas for 2 time periods (1973-80 and 1981-87) and percent change between periods by sex and age, all SEER areas combined.

	All Ages			<20			20 - 39			40 - 79		
	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change
Bone & Joint	672	602										
Both sexes	0.84 (1162)	0.88 (1099)	+5	0.80 (373)	0.94 (334)	+18	0.60 (254)	0.61 (265)	+2	1.00 (472)	0.97 (445)	-3
Males	1.00 (666)	1.04 (628)	+4	0.87 (209)	1.07 (195)	+23	0.75 (159)	0.77 (168)	+3	1.28 (276)	1.19 (248)	-7
Females	0.69 (496)	0.73 (471)	+6	0.72 (164)	0.81 (139)	+13	0.46 (95)	0.44 (97)	-4	0.76 (196)	0.81 (197)	+7
Osteosarcoma												
Both sexes	0.30 (404)	0.31 (370)	+3	0.37 (175)	0.46 (163)	+24	0.20 (85)	0.19 (82)	-5	0.27 (128)	0.24 (109)	-11
Males	0.33 (215)	0.39 (226)	+18	0.36 (88)	0.55 (100)	+53	0.21 (45)	0.25 (53)	+19	0.37 (79)	0.32 (68)	-14
Females	0.27 (189)	0.24 (144)	-11	0.38 (87)	0.37 (63)	-3	0.19 (40)	0.14 (29)	-26	0.19 (49)	0.17 (41)	-11

[a] Cases per 100,000 population per year, age-adjusted based on the 1970 U.S. Population.

TABLE 2

Average annual age-adjusted incidence rates[a] (# of cases) for bone and joint cancers in both sexes for 2 time periods (1973-80 and 1981-87) and percent change between periods by age and fluoridation status, all SEER areas combined.

	All Ages			<20			20 - 39			40 - 79		
	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change
"Non-Fluoridated" SEER	0.90 (156)	0.85 (153)	-6	0.85 (56)	0.88 (55)	+4	0.62 (34)	0.49 (31)	-21	1.13 (61)	1.04 (61)	-10
"Fluoridated" SEER	0.84 (553)	0.91 (511)	+8	0.82 (175)	1.08 (166)	+32	0.57 (116)	0.54 (114)	-5	0.99 (228)	0.94 (221)	-5
<1955	0.90 (91)	0.86 (76)	-4	0.57 (16)	0.91 (18)	+60	0.78 (26)	0.55 (19)	-29	1.35 (47)	0.93 (29)	-26
≥1966	0.83 (395)	0.93 (373)	+12	0.89 (141)	1.07 (118)	+20	0.55 (79)	0.60 (84)	+9	0.88 (150)	0.96 (149)	+9

[a] Cases per 100,000 population per year, age-adjusted based on the 1970 U.S. Population.

TABLE 3

Average annual age-adjusted incidence rates[a] (# of cases) for bone and joint cancers in males for 2 time periods (1973-80 and 1981-87) and percent change between periods by age and fluoridation status, all SEER areas combined.

	All Ages			<20			20 - 39			40 - 79		
	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change
"Non-Fluoridated SEER	0.98 (83)	0.83 (73)	-15	0.71 (24)	0.69 (22)	-5	0.78 (22)	0.57 (18)	-28	1.38 (35)	1.17 (32)	-15
"Fluoridated" SEER	1.02 (318)	1.12 (299)	+10	0.97 (106)	1.35 (107)	+39	0.72 (73)	0.70 (73)	-3	1.26 (130)	1.13 (110)	-10
<1955	1.23 (58)	1.18 (48)	-4	0.88 (12)	1.22 (12)	+39	0.84 (15)	0.85 (15)	+1	1.97 (31)	1.39 (20)	-29
≥1966	1.00 (228)	1.10 (209)	+10	1.03 (84)	1.35 (77)	+31	0.70 (50)	0.71 (50)	+1	1.13 (86)	1.06 (75)	-6

[a] Cases per 100,000 population per year, age-adjused based on the 1970 U.S. Population.

TABLE 4

Average annual age-adjusted incidence rates[a] (# of cases) for osteosarcoma in males for 2 time periods (1973-80 and 1981-87) and percent change between periods by age and fluoridation status, all SEER areas combined.

	All Ages			<20			20 - 39			40 - 79		
	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change	73-80	81-87	Change
"Non-Fluoridated" SEER	0.29 (25)	0.30 (26)	+3	0.30 (10)	0.42(13)	+40	0.29 (8)	0.15 (5)	-48	0.29 (7)	0.25 (7)	-14
"Fluoridated" SEER	0.33 (103)	0.44 (112)	+3	30.39 (43)	0.66 (52)	+69	0.21 (21)	0.25 (25)	+19	0.37 (37)	0.34 (33)	-8
<1955	0.32 (16)	0.42 (14)	+31	0.22 (3)	0.73 (7)	+232	0.32 (6)	0.18 (3)	-44	0.44 (7)	0.27 (4)	-39
≥1966	0.35 (98)	0.45 (82)	+29	0.44 (36)	0.66 (38)	+50	0.19 (13)	0.29 (19)	+53	0.37 (27)	0.32 (23)	-14

[a] Cases per 100,000 population per year, age-adjusted based on the 1970 U.S. Population.

TABLE 5

Observed to expected[a] incidence ratios (# of observed) by duration of fluoridation or age, whichever is less, for selected sex and cancer-site groupings for those under age 20 at diagnosis ("fluoridated" counties, Seattle and Iowa SEER registries).

		Duration of Fluoridation (yrs.)			
Site	Sex	<5	5-9	10-14	15-19
Bones & Joints	Both	1.7 (11)	1.1 (21)	1.4 (38)	1.3 (25)
Osteosarcoma	Both	1.6 (4)	1.8 (11)	1.0 (16)	0.9 (13)
	Males	1.0 (1)	2.9 (9)	0.7 (8)	0.4 (5)

[a] Expected based on the rates in "non-fluoridated" counties adjusted for age, calendar time, and geographic area.

TABLE 6

Observed to expected[a] incidence ratios (# of observed) by duration of fluoridation or age, whichever is less, for selected sex and cancer-site groupings for those under age 20 at diagnosis ("Fluoridated" counties, all SEER areas).

		Duration of Fluoridation (yrs.)			
Site	Sex	<5	5-9	10-14	15-19
Bones & Joints	Both	1.3 (27)	0.9 (104)	1.2 (142)	1.0 (67)
Osteosarcoma	Both	1.4 (10)	1.2 (52)	1.2 (70)	1.0 (34)
	Males	1.7 (4)	1.5 (30)	1.7 (41)	1.0 (20)

[a] Expected based on the rates in "non-fluoridated" counties adjusted for age and calendar time.