Original Article

Dental X-Rays and Risk of Meningioma

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BACKGROUND: Ionizing radiation is a consistently identified and potentially modifiable risk factor for meningioma, which is the most frequently reported primary brain tumor in the United States. The objective of this study was to examine the association between dental x-rays—the most common artificial source of ionizing radiation—and the risk of intracranial meningioma. **METHODS:** This population-based case-control study included 1433 patients who had intracranial meningioma diagnosed at ages 20 to 79 years and were residents of the states of Connecticut, Massachusetts, North Carolina, the San Francisco Bay Area, and 8 counties in Houston, Texas between May 1, 2006 and April 28, 2011 (cases). A control group of 1350 individuals was frequency matched on age, sex, and geography (controls). The main outcome measure for the study was the association between a diagnosis of intracranial meningioma and self-reported bitewing, full-mouth, and panorex dental x-rays. **RESULTS:** Over a lifetime, cases were more than twice as likely as controls (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.4-2.9) to report having ever had a bitewing examination. Regardless of the age at which the films were obtained, individuals who reported receiving bitewing films on a yearly basis or with greater frequency had an elevated risk for ages <10 years (OR, 1.4; 95% CI, 1.0-1.8), ages 10 to 19 years (OR, 1.6; 95% CI, 1.2-2.0), ages 20 to 49 years (OR, 1.9; 95% CI, 1.4-2.6), and ages ≥40 years (OR, 1.5; 95% CI, 1.1-2.0). An increased risk of meningioma also was associated with panorex films taken at a young age or on a yearly basis or with greater frequency, and individuals who reported receiving such films at ages <10 years had a 4.9 times increased risk (95% CI, 1.8-13.2) of meningioma. No association was appreciated for tumor location above or below the tentorium. **CONCLUSIONS:** Exposure to some dental x-rays performed in the past, when radiation exposure was greater than in the current era, appears to be associated with an increased risk of intracranial meningioma. As with all sources of artificial ionizing radiation, considered use of this modifiable risk factor may be of benefit to patients. ***Cancer* 2012;000:000–000.**© *2012American Cancer Society.*

KEYWORDS: meningioma, epidemiology, risk factors, brain tumor, genetics, ionizing radiation, dental x-rays, diagnostic x-rays.

INTRODUCTION

Meningiomas accounted for 33.8% of all primary brain and central nervous system (CNS) tumors reported in the United States between 2004 and 2006 and, thus, represent the most frequently diagnosed primary brain tumor in adults.[1] Despite this, few studies exist that examine risk factors for this lesion, which frequently is associated with neurologic complications and decreased quality of life.[2]

The most consistent environmental risk factor identified for meningioma is exposure to ionizing radiation (IR), with relative risks from 6-fold to 10-fold reported.[3-8] However, most studies of IR and meningioma risk include individuals who were exposed to high levels of radiation from sources such as atomic bombs[5,6] or treatment for oncologic and other medical conditions.[3,4] Studies that examine risk associated with the lower dose exposures more likely to be experienced in

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All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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the general population are limited in number, include fewer than 200 cases each, and focus on exposure to dental x-rays.[9-17] To our knowledge, no studies have reported on the association between use of computed tomography (CT) and meningioma risk. The studies that report on dental x-ray exposure are suggestive but are limited by sample size and by the inclusion of cases from time periods with higher dosing regimes than the current era.[9-17] Several case-control studies in the United States exist; The first of these included cases diagnosed between 1980 and 1984 in Los Angeles County, California, and reported a significantly increased risk for women associated with a first full-mouth series obtained before age 20 years or before 1945[15] as well as an increased but nonsignificant risk for men who had $\geq$5 full-mouth series before 1945.[10] More recently, Longstreth et al[12] examined 200 cases diagnosed between 1995 and 1998 in Washington State and reported that a history of $\geq$6 full-mouth series was associated with increased risk (odds ratio [OR], 2.06; 95% confidence interval [CI], 1.03-4.17) but found no evidence for a dose-response relation (P for trend = .33).[12] No recent large-scale studies of meningioma risk relative to common IR exposure exist, when doses for dental and other procedures have decreased but during which time new radiographic procedures have been introduced, including CT. In this report, we compare dental and therapeutic radiation histories in 1433 patients with those from a group of 1350 controls. The large sample size afforded by this population-based study will help to provide a more precise estimate of any association, particularly for the lower exposure levels experienced by more recently diagnosed cases.

MATERIALS AND METHODS

Study Design

Eligible patients included all individuals who were diagnosed from May 1, 2006 to April 28, 2011 who had histologically confirmed intracranial meningioma among residents of the states of Connecticut, Massachusetts, and North Carolina as well as 6 counties in the state of California (Alameda, San Francisco, Contra Costa, Marin, San Mateo, and Santa Clara) and 8 counties in the state of Texas (Brazoria, Fort Bend, Harris, Montgomery, Chambers, Galveston, Liberty, and Waller). These patients (the case group) were identified through the Rapid Case Ascertainment (RCA) systems and state cancer registries of the respective sites and were between ages 20 and 79 years at the time of diagnosis. The control group was selected with random-digit-dialing by an outside consulting firm (Krieder Research, Orono, Me) and were matched to cases by 5-year age interval, sex, and state of residence. Study participants who had a previous history of meningioma and/or a brain lesion of unknown outcome were excluded. Participants were English-speaking or Spanish-speaking. The study, consent forms, and questionnaire were approved by the Human Investigation Committees at the Yale University School of Medicine, Brigham and Women's Hospital, the University of California at San Francisco, the University of Texas M. D. Anderson Cancer Center, and the Duke University School of Medicine. The study also was approved by the State of Connecticut Department of Public Health Human Investigation Committee, and some data were obtained directly from the Connecticut Tumor Registry in the Connecticut Department of Public Health as well as from the Massachusetts Tumor Registry.

Data Collection

The physicians of each eligible case were contacted to request permission to approach the patient. Cases who were approved for contact by their physicians and the controls identified by Krieder Research were sent an introductory letter. Approximately 1 to 2 weeks later, a trained interviewer contacted the potential study participant by telephone to administer the interview. Interviews took an average of 52 minutes. Proxies provided information for 9 cases and no controls. The questionnaire included detailed questions on demographics, family history of cancer, pregnancy and menstrual history, exogenous hormone history, and medical history, including therapeutic and diagnostic radiation procedures. Participants were questioned about the onset, frequency, and type of dental care received over their lifetime, including orthodontic work, endodontic (root canal) work, dental implants, and dentures. Participants were asked to report the number of times they had received bitewing, full-mouth, or panoramic (panorex) films during 4 periods: when aged $<$10 years, ages 10 to 19 years, ages 20 to 49 years, and aged $\geq$50 years. Information also was gathered on the occurrence and timing of therapeutic radiation treatments, specifically radiation or radium treatments to the face, head, neck, or chest for both benign and malignant lesions or conditions. Risk factor and screening information was truncated at the date of diagnosis for cases and at the date of interview for controls (hereafter referred to as the *reference date*).

To date, 2228 eligible cases and 2604 eligible controls have been identified. Ninety-eight percent of eligible

cases had a consenting physician. Among those cases, 65% participated in the interview portion of the study, whereas 52% of eligible controls participated in the interview. Six hundred sixty-six cases were ineligible because of out-of-state residency (n = 45), language (n = 70), recurrent meningioma (n = 83), incarceration (n = 3), age (n = 50), spinal meningioma (n = 144), pathology unavailable for review (n = 56), mental or medical (ie, deaf) illness (n = 96), death (cause of death other than meningioma; n = 76), another pathology (ie, lung metastasis; n = 16), or other (n = 27). Eighty-five controls were ineligible because of out-of-state residency (n = 6), language (n = 8), a history of previous brain tumor with unknown pathology (n = 8), age group (n = 1), mental or medical illness (n = 53), death (n = 3), or other (n = 8). The sample that was used in this analysis included 1433 cases and 1350 controls.

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. *T* tests, chi-square tests, and Fisher exact tests were used to examine associations between the risk of meningioma and independent covariates. To assess the odds of meningioma associated with risk factors, conditional logistic regression was used to provide maximum-likelihood estimates of the OR (adjusted for age, sex, race [white vs nonwhite], education [$\leq$16 years of education vs >16 years], and history of head CT) with 95% CIs using the statistical package PC-SAS version 9.2 (SAS Institute, Inc., Cary, NC).[18] To avoid attributing the effect of therapeutic IR to dental x-rays, individuals who had received therapeutic radiation to the head, neck, chest, or face were removed from all analyses that assessed the risk associated with dental x-rays. To assess the association by anatomic location of the meningiomas, we also performed subanalyses by dividing cases into those with meningiomas located above or below the tentorium as well as those with skull base tumors using imaging and operative reports.

RESULTS

Descriptive statistics are provided in Table 1. The mean age was 57.5 years for cases versus 57.4 years for controls ($P = 0.74$). The majority of study participants were women and were white. Cases and controls did not differ according to age, race, sex, or geographic location. Controls were more likely to have $\geq$16 years of education and to have an annual salary >$75,000.

Dental X-Rays

Table 2 compares reported dental care and imaging histories for cases and controls. All but 1 control and 2 cases reported having visited a dentist on at least 1 occasion, although cases were less likely to report seeing a dentist on a yearly basis. Controls reported first seeing a dentist at a younger age than cases (8.6 years vs 9.6 years, respectively; $P < .01$). Cases and controls reported no differences in use of orthodontics or endodontics, but cases were less likely to report having dentures (OR, 0.8; 95% CI, 0.6-1.0) and were more likely to report dental implants (OR, 1.3; 95% CI, 1.0-1.7) relative to controls.

The majority of study participants reported having had at least 1 bitewing in their life (95.8% of cases and 92.2% of controls), whereas approximately 75% of study participants reported having undergone at least 1 full-mouth series. Over a lifetime, cases were more than twice as likely as controls to report having ever had a bitewing. Significantly elevated risk was observed across all ages with the exception of individuals aged $\geq$50 years at the time of bitewing, although the elevated risk estimate for this age group was similar to that for younger individuals. Regardless of the age, more frequent receipt of bitewing films was associated with increased risk. A similar (but not statistically significant) elevated risk for meningioma was observed for full-mouth series among individuals who received yearly or more frequent scans at a young age.

The use of panorex films was less frequently reported than for bitewing or full-mouth series (approximately 47% of study participants), as expected. Significant increases in the risk of meningioma was associated with young age at receipt of screening as well as more frequent screening, and individuals who were aged <10 years at the time of screening had an almost 5-fold increase in risk (OR, 4.9; 95% CI, 1.8-13.2).

It is noteworthy that cases were no more likely to have received a head CT (before their diagnosis of meningioma) than controls (OR, 1.0; 95% CI, 0.8-1.1). Very few individuals had received a cerebral angiogram (17 cases and 18 controls; $P = .7$). No association was observed between tumor location (supratentorial vs infratentorial) and dental x-rays.

Therapeutic Radiation

One hundred seventy-four participants (114 cases and 60 controls) reported that they received previous radiation therapy to the head, neck, face, or chest (Table 3). Cases were more likely to have received such radiation overall (OR, 1.8; 95% CI, 1.3-2.5). Cases were 1.5 times more

Table 1. Descriptive Statistics of the Study Sample

	Cases, n = 1433		Controls, n = 1350		
Variable	No.	%	No.	%	*P* (Cases vs Controls)
Age, y					
20-29	24	1.7	20	1.5	
30-39	89	6.2	87	6.5	
40-49	271	18.9	252	18.7	
50-59	405	28.3	410	30.5	
60-69	435	30.4	356	26.5	
70-79	208	14.4	220	16.3	
Mean±SD	57.5±11.7		57.4±12.0		.74
Sex					
Men	384	26.8	392	29	
Women	1049	73.2	958	71	.19
Race					
White	1191	83.1	1157	85.7	
Black	114	8	61	4.5	
Asian	51	3.6	51	3.8	
Other	67	5.3	81	6	.08
Residence					
Connecticut	147	10.3	167	12.4	
Massachusetts	314	21.9	321	23.8	
North Carolina	424	29.6	394	29.2	
California	366	25.4	317	23.5	
Texas	182	12.7	151	11.2	.17
Education					
≤16 y	386	27.1	238	17.7	<.01
>16 y	1041	72.9	1109	82.3	
Income					
≤$75,000	720	57.2	590	48.6	<.01
>$75,000	538	42.8	624	51.4	

Abbreviations: SD, standard deviation.

likely (95% CI, 1.0-2.2) and 2.8 times more likely (95% CI, 1.0-7.8) than controls to report receiving radiation for a malignant or benign tumor, respectively.

DISCUSSION

To our knowledge, this is the largest case-control study to date examining the correlation between dental x-rays and the risk of meningioma; and, because it is the most recent study, it provides an improved examination of the effects of reduced dosing exposure levels over time. Our findings suggest that dental x-rays, particularly when obtained frequently and at a young age, may be associated with an increased risk of intracranial meningioma, at least for the dosing received by our study participants. Earlier analyses based primarily on data drawn from smaller cohorts of patients (and who likely were exposed to higher IR doses) also reported an increased risk with dental x-rays primarily for the higher dose, full-mouth series but only when received at high frequency or a young age.[10,12,15] In their population-based case-control study, which included 200 patients with meningioma, Longstreth et al observed an association for those who reported ≥6 full-mouth films (OR, 2.06; 95% CI, 1.03-4.07) but not for those who reported fewer films or bitewing or panorex films.[12] Preston-Martin et al reported an increased risk for women who received a full-mouth series before age 20 years or before 1945; however, this was the only type of x-ray examined.[15] Our findings indicate a statistically significant increased risk with both bitewing and panoramic films. Risk estimates for full-mouth films, although not statistically significant, were consistently in the same direction as for the other 2 film types. Both Longstreth et al[12] and Preston-Martin et al[15] reported that the highest

Table 2. Dental X-Ray Histories of Meningioma Cases and Controls[a]

Variable	Cases, n = 1433		Controls, n = 1350		
	No.	%	No.	%	OR (95% CI)[b]
Dental x-rays					
Orthodontic/braces	380	28.8	403	33.3	0.9 (0.8-1.1)
Endodontic/root canal	768	58.3	709	58.6	1.0 (0.9-1.2)
Dental implants	140	10.6	109	9	1.3 (1.0-1.7)
Dentures	250	18.9	234	19.3	0.8 (0.6-1.0)
Yearly dental visits: Yes/No	1034	78.3	1026	84.3	0.8 (0.6-0.9)
Ever had bitewing					
Aged <10 y	239	27.5	209	23.3	1.3 (1.0-1.7)
Ages 10-19 y	682	66.6	620	61.2	1.4 (1.1-1.7)
Ages 20-49 y	1048	91.4	964	87.5	1.7 (1.3-2.2)
Aged ≥50 y	698	83.4	677	82.7	1.2 (0.9-1.6)
Any age	1127	95.8	1043	92.2	2.0 (1.4-2.9)
Frequency of bitewings					
Aged <10 y					
None	631	72.5	692	76.8	1.0
Less than yearly	109	12.5	97	10.8	1.3 (1.0-1.8)
Yearly or more	130	14.9	112	12.4	1.4 (1.0-1.8)
Ages 10-19 y					
None	342	33.4	393	38.8	1.0
Less than yearly	368	35.9	357	35.2	1.3 (1.1-1.6)
Yearly or more	314	30.7	263	25.9	1.6 (1.2-2.0)
Ages 20-49 y					
None	98	8.6	138	12.5	1.0
Less than yearly	627	54.7	625	56.7	1.6 (1.2-2.1)
Yearly or more	421	36.7	339	30.8	1.9 (1.4-2.6)
Aged ≥50 y					
None	135	16.2	142	17.3	1.0
Less than yearly	370	44.4	406	49.6	1.1 (0.8-1.4)
Yearly or more	328	39.4	271	33.1	1.5 (1.1-2.0)
Ever had full mouth					
Aged <10 y	100	11	90	9.3	1.2 (0.8-1.7)
Ages 10-19 y	371	36.5	352	34.8	1.1 (0.9-1.4)
Ages 20-49 y	738	66.1	706	65.4	1.0 (0.9-1.2)
Aged ≥50 y	488	59.7	469	58.2	1.1 (0.9-1.4)
Any age	864	75.5	833	75	1.0 (0.9-1.3)
Frequency of full mouth					
Aged <10 y					
None	805	88.9	882	90.7	1.0
Less than yearly	69	7.6	64	6.6	1.2 (0.8-1.7)
Yearly or more	31	3.4	26	2.7	1.3 (0.8-2.3)
Ages 10-19 y					
None	644	63.4	660	65.2	1.0
Less than yearly	277	27.3	274	27.1	1.1 (0.9,1.4)
Yearly or more	94	9.3	78	7.1	1.2 (0.9,1.8)
Ages 20-49 y					
None	379	33.9	374	34.6	1.0
Less than yearly	608	54.4	593	54.9	1.0 (0.8-1.2)
Yearly or more	130	11.6	113	10.5	1.1 (0.8-1.5)
Aged ≥50 y					
None	329	40.3	337	41.8	1.0
Less than yearly	381	46.6	367	45.5	1.1 (0.9-1.4)
Yearly or more	107	13.1	102	12.7	1.1 (0.8-1.6)

(Continued)

Table 2. (Continued)

Variable	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)[b]
Ever had Panorex					
Aged <10 y	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y	91	8	69	6.1	1.5 (1.1-2.1)
Ages 20-49 y	349	30.3	355	31.5	0.9 (0.7-1.1)
Aged ≥50 y	253	29.9	223	27	1.2 (0.9-1.5)
Any age	536	46.7	541	46.7	1.0 (0.8-1.2)
Frequency of Panorex					
Aged <10 y					
Ever	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y					
None	1040	92	1054	93.7	1.0
Less than yearly	74	6.5	63	5.6	1.3 (0.9-1.9)
Yearly or more	17	1.5	6	0.5	3.0 (1.2-7.8)
Ages 20-49 y					
None	803	69.7	773	68.5	1.0
Less than yearly	311	27	341	30.2	0.9 (0.7-1.0)
Yearly or more	38	3.3	14	1.2	2.7 (1.4-5.3)
Aged ≥50 y					
None	592	70.1	603	73	1.0
Less than yearly	214	25.3	209	25.3	1.0 (0.8-1.3)
Yearly or more	39	4.6	14	1.7	3.0 (1.6-5.6)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Individuals who received therapeutic radiation to the head, neck, face, or chest were not included (114 cases and 60 controls).
[b] Adjusted for age, sex, education, race (white vs nonwhite), and history of head computed tomography.

Table 3. Reported History of Therapeutic Radiation to Head, Neck, Face, or Chest Among Meningioma Cases and Controls

Radiation Treatment For	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)
Cancer	58	4.1	37	2.7	1.5 (1.0-2.2)[a]
Benign tumor	15	1	5	0.4	2.8 (1.0-7.8)[a]
Tonsils/adenoids	5	0.4	0	0	$P = .0628$[b]
Thyroid	9	0.6	2	0.2	$P = .0660$[b]
Acne	10	0.7	6	0.4	$P = .4565$[b]
Ringworm	4	0.4	0	0	$P = .1253$[b]
Ear	3	0.2	1	0.1	$P = .6254$[b]
Other	15	1.1	9	0.7	$P = .3087$[b]
Any	114	8	60	4.4	1.8 (1.3-2.5)[a]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, sex, and race (white vs nonwhite).
[b] Fisher exact test (2-sided probability).

risk for full-mouth series was observed in young patients with higher exposure levels. Given the possible error in recall of specific numbers of dental x-rays, we restricted our frequency analyses to yearly or greater versus less than yearly. It is noteworthy that the percentages of individuals reporting each of the 3 categories of x-ray in our series match well to the previous studies.

Strengths of this study include the population-based study design, the large sample size (which may have allowed us to detect effects for x-rays with lower effective

dose), and the relatively consistent magnitude and direction of risk estimates. Histologic confirmation was obtained for all cases, suggesting that these results may only be applicable to lesions that are deemed in need of surgery rather than conservative management.

Limitations of this study include the possibility of either under-reporting or over-reporting of dental x-rays by study participants. This is a difficult problem in epidemiology, because, unlike medical care, which (at least within cohorts of patients drawn from health maintenance organizations or similar entities) may be confirmed by a review of centralized medical records, dental care generally is obtained (even for a single individual) from numerous dentists, all of which are outside of a health maintenance organization or hospital-based setting, providing little opportunity for researchers to validate dental reports in a timely or cost-efficient manner. No national database of dental treatment exists within the United States; hence, researchers must rely on patient self-report, despite the potential for bias. In the largest (n = 200) previous case-control study to date of dental x-rays and meningioma (Longstreth et al, 2004), researchers validated dental information on 72 cases and 75 controls, estimating that cases and controls saw 6.1 and 6.6 dentists, respectively, over a lifetime.[12,19] Participants recalled bitewing and panoramic x-rays more accurately than full-mouth series, which they over-reported. The extent of the over-reporting varied by age and was greater for cases for recent visits and greater for controls for visits more distant in time. However, participants recalled 81% of the dentists visited in their lifetime, and the majority of forgotten dentists and dental care procedures involved only 1 or 2 visits.[12,19] A second validation effort[20] revealed that, although both cases and controls tended to overestimate the number of dental x-ray visits, recall appeared to be unbiased with measures of agreement between interview and dental chart data similar for cases and controls.

The extent to which the risk of meningiomas associated with exposure to IR is modified by genotype is a research area of intense interest. Genetic variants in genes involved in the DNA repair pathway, some of which appear common to several tumor types, have been implicated in meningioma risk but have not been confirmed.[21-24] Data from Israel provide evidence for genetic predisposition to radiation-associated meningioma,[22-24] highlighting the role of inherited genetic factors as well as exposure in the development of meningioma. As radiation exposure is in many instances avoidable, the need to identify high-risk genetic variants is of great importance to potentially decrease the risk of meningiomas and probably other tumors. Studies like these allow for the collection of large numbers of individuals with various gene*environment combinations and, hence, comparison of the effect of exposures like IR across genetic variants; our group plans to further examine these interactions.

The findings presented here are important, because dental x-rays remain the most common artificial source of exposure to IR for individuals living in the United States. The use of other medical imaging procedures (and, hence, exposure to IR) is on the rise,[25] with the National Council on Radiation Protection and Measurements reporting that the per capita dose of radiation from medical imaging has increased by a factor of approximately 6 since the early 1980s.[26] For the most part, these procedures are associated with even higher levels of exposure to IR than are bitewing or full-mouth dental x-rays. These statistics are noteworthy: The primary environmental (and generally modifiable) risk factor consistently identified for meningioma is exposure to IR. The American Dental Association's recent statement[27] on the use of dental radiographs highlights the need for dentists to examine the risk/benefit ratio associated with the use of dental x-rays and confirms that there is little evidence to support the use of dental x-rays to search for occult disease in asymptomatic patients or to obtain routine dental studies from all patients at preset intervals. Although dental x-rays are an important tool in well selected patients, efforts to moderate exposure to IR to the head is likely to be of benefit to patients and health care providers alike.

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