Neuro-Oncology 13(3):345–352, 2011.
doi:10.1093/neuonc/noq201

Possible interaction between ionizing radiation, smoking, and gender in the causation of meningioma

Pazit Flint-Richter, Lori Mandelzweig, Bernice Oberman, and Siegal Sadetzki

Cancer and Radiation Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel (P.F.-R., L.M., B.O., S.S.); Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel (S.S.)

Data on the association between smoking and meningioma are inconsistent. The aim of this study was to assess the role of smoking in radiation- and non–radiation-related meningiomas. The study was designed as a 4-group case-control study, balanced for irradiation, including 160 irradiated meningioma case patients, 145 irradiated control subjects, 82 nonirradiated case patients, and 135 nonirradiated control subjects. The sources of these groups included a cohort of individuals who underwent radiotherapy (mean dose, 1.5 Gy to the brain) during childhood for treatment of tinea capitis, claims filed for radiation damage in the framework of a compensation law, and the Israel Cancer Registry. All tests of statistical significance were 2-sided. A statistically significantly elevated risk of meningioma was found among men who had ever smoked, compared with those who were never smokers (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.09-4.15), increasing with smoking pack-years from 1.67 to 2.69 for <10 to >20 pack-years, respectively. Among women, an interaction between radiation and smoking was observed, expressed by a significant protective efect for meningioma (OR, 0.32; 95% CI, 0.14-0.77), with a strong dose-response association ($P < .01$) in nonirradiated women and a nonsignificant increased risk of meningioma among those who were irradiated (OR, 1.23; 95% CI, 0.68-2.23). Variation in the association between smoking and meningioma may be explained by effects of distinct host factors, such as past exposure to ionizing radiation and/or hormonal factors.

Keywords: ionizing radiation, smoking, meningioma.

Received August 29, 2010; accepted November 20, 2010.

Correspondence Author: Siegal Sadetzki, MD, Cancer and Radiation Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer 52621, Israel (siegals@gertner.health.gov.il).

The concept of multifactorial causation, in which environmental, intrinsic, and genetic factors interact to influence outcome, is recognized as a valid scientific paradigm for the etiology of chronic diseases.

Little is known about the etiology of meningiomas, with ionizing radiation being the only environmental factor that has been shown unequivocally to be a causative factor.[1–6] A publication by our group reported an estimated excess relative risk/Gy (ERR/Gy) of 4.63 (95% confidence interval [CI], 2.43-9.12) for meningioma, following childhood exposure of about 140 centiGy to the brain.[6] This estimate is based on 40 years of follow-up of a cohort which includes a group of 10,842 individuals who were treated during childhood in Israel during the 1950s with radiation therapy for tinea capitis (TC) and 2 comparison groups which comprised a non irradiated population ($n = 10,842$) and sibling ($n = 5392$) controls. Although the extensive public health campaign aimed at eradicating TC in the 1950s included both Jewish and Arab individuals who were treated in Israel and Jewish individuals who were treated abroad, mainly in north African and Middle Eastern countries prior to their immigration to Israel, the TC cohort includes only a subset of those who were treated in Israel. On the basis of the aforementioned results, a law was established in 1994, for the purpose of compensating irradiated individuals who had developed specific diseases that were proven to be causally associated with the irradiation given as treatment for TC.

Smoking is known to be a powerful carcinogen that is involved in the etiology of many cancers, including cancers of the lung, bladder, pancreas, stomach, esophagus, kidney, larynx, oral cavity and pharynx, leukemia, and cervix.[7] The relationship between smoking and meningiomas has been assessed in a few studies, but the results are inconsistent. Cigarette smoking was positively associated with meningioma risk in women but not in men in a hospital case-control study conducted in China. Smoking pack-years above the median for

women yielded a significant increased odds ratio (OR) of ~ 6 (95% CI, 2.04-18.87).[8] In contrast, a population, based case-control study from Washington state found that any positive history of smoking was associated with a significantly increased risk of meningioma in men and a decreased risk in women.[9] A study that included women only reported smoking to be an independent protective factor for meningioma among premenopausal women.[10] In other studies, no association between active smoking and meningiomas was apparent.[11–17]

The aim of this study was to assess the role of smoking in the development of meningioma and, in particular, its possible interaction with another potent carcinogen, ionizing radiation.

Materials and Methods

Study population

The study was designed as a case-control study balanced for irradiation. The total study population comprised 522 subjects divided into 4 groups: 160 case patients who were irradiated for TC in childhood and subsequently developed meningioma (radiation-associated meningioma [RAM]), 145 subjects who were irradiated for TC but did not develop meningioma (irradiated control subjects), 82 case patients with meningioma with no previous history of radiation exposure (non-RAM), and 135 subjects who were not irradiated and did not develop meningioma (nonirradiated control subjects).

Recruitment of the study participants

The RAM group was identified from 2 sources: the TC cohort and the TC compensation law.[1,18] The TC cohort was linked to the Israel Cancer Registry (ICR) to update diagnoses of meningioma using the International Classification of Diseases for Oncology topography codes C70.0 and C70.9 and morphology codes 953.0-953.9. The ICR was established in 1960 and is notified by law of information on all malignant tumors, as well as benign meningiomas. Additional irradiated case patients were identified from the claim files, which include information on medical diagnoses.

Originally, data on 530 previously irradiated case patients with meningioma were collected from the aforementioned sources. To ensure unequivocally that the RAM group in the analysis included only irradiated individuals, 178 of the case patients identified from the claim files were excluded from the initial group due to insufficient validation of previous irradiation exposure. Of the remaining 351 patients, 28 were deceased, 36 could not be located, 25 could not participate due to their medical condition, and 41 were excluded because their residence addresses were out of the geographical area of the study. For the remaining group of 222 patients, verification of irradiation was based on the following criteria: appearance in the original TC cohort ($n = 78$), documentation of scalp irradiation which was reported by the patient to the treating physician at least 1 year prior to implementation of the compensation law ($n = 62$), approval of the claim of irradiation by a professional dermatologist and/or expert committee ($n = 70$), photographic evidence documenting irradiation treatment in childhood ($n = 1$), or original certification from the treating center ($n = 1$). Patients identified from the ICR who reported a previous irradiation treatment but did not file claims for compensation ($n = 10$) were also included in the study. The compliance rate among eligible RAM case patients who were targeted for enrollment in the study was 72%.

The non-RAM group was identified through the ICR. To validate whether potential non-RAM case patients had a previous history of irradiation to the head area, short preliminary telephone interviews were conducted for all candidate non-RAM case patients. Overall, 111 patients with meningioma were included in the target population of this non-RAM group; 77% of them participated in the current analysis.

Healthy control subjects (irradiated and nonirradiated groups) were recruited from the exposed and nonexposed groups of the original TC cohort. Control subjects were individually matched to the case patients by sex, year of birth (± 2 years), and country of origin. The compliance rates among eligible subjects who were targeted for enrollment in the study were 74% and 63% for irradiated and nonirradiated control subjects, respectively.

In the process of ascertainment of the non-RAM case patients, we found that a substantial number of the patients with meningioma who were born during the 1950s and were of Asian-African origin reported irradiation treatment for TC. This limited our ability to find enough nonirradiated case patients of this origin who met the original matching criteria for age.[6,19] Therefore we extended the matching criteria for the year of birth to ± 10 years for the non-RAM group.

Dosimetry

The therapeutic procedure for TC followed the Adamson–Kienbock technique. The hair was shaved, and the scalp area was divided into 5 fields that were irradiated over 5 consecutive days. The remaining hair was removed through a waxing process.

The irradiation was performed with a 75-100 kilovolt superficial therapy x-ray machine. The children were exposed to 3.5-4 Gy per field, at a Focus Skin Distance of 25-30 cm.[2] Most of the individuals received 1 course of therapy, but ~ 9% of the patients received ≥ 2 treatments. Dosimetric studies that were conducted using one of the original x-ray machines, and a head phantom estimated the average dose to the brain as 1.5 Gy (range, 1.0-6.0 Gy). Doses were also calculated for different areas of the brain; the lowest average dose was for the back and front of the lower plane (mean, 1.1 Gy), whereas the highest dose was for the front of the upper plane (mean, 1.8 Gy).[2,20]

More details on the methodology of the TC studies in general, on dosimetry, and on this study specifically are available in previous publications.[2,6,18,20]

Data collection

The study protocol was approved by the Sheba Medical Center Institutional Review Board. Recruitment began by contacting the target population by telephone and explaining the goals and methods of the study. The rates of subjects who were lost to follow-up in the study were 13.8%, 17.8%, 24.5%, and 23.5% in the RAM, non-RAM, irradiated control, and nonirradiated control groups, respectively.

Data were collected in face-to-face interviews using questionnaires that included demographic variables, exposure to environmental hazards (eg, smoking and alcohol use), occupational and medical exposure to ionizing radiation, personal medical diagnoses and family history of cancer and benign tumors, previous exposures to radiation, head injuries, and hormonal factors. Validation of diagnoses for all cases was performed using the original pathology, imaging, or surgery reports.

Data analysis and statistical methods

Reference dates for all exposures were defined as the age at diagnosis minus 2 years of latent period for cases and as the reference date of the matched case for each control.

For each subject who reported smoking, we calculated the number of pack-years of exposure (1 pack-year is equivalent to smoking 1 pack per day for one year).

Conditional logistic regression was used to estimate ORs with corresponding 95% CIs. A potential interaction between the tested variable and radiation exposure was assessed using models that included the main effect of the radiation, main effect of the tested variable, and the interaction term. When the P value for interaction was $< .1$, separate estimates of the OR were calculated for irradiated and nonirradiated case-control groups.

Statistical analysis was conducted using the S-Plus software.[21] All tests of statistical significance were 2-sided.

Results

Demographic characteristics of the study population are listed in Table 1. Approximately 30% of the study population was male, mostly of African-Asian origin. The mean ages at diagnosis of the meningiomas were 45.9 and 48.5 years for irradiated and nonirradiated case patients, respectively. Both groups of case patients were interviewed, on average, 10 years after diagnosis (mean $\pm$ standard deviation [SD], 9.6 ± 7.0 years in the irradiated group and 10.9 ± 7.5 in the nonirradiated group, $P = .15$, data not shown). The mean age ($\pm$ SD) at interview of the total study population was 56.1 ± 5.7 years (range, 45-74 years). Nonirradiated case patients were significantly older than nonirradiated control subjects (60.0 vs 56.1 years, respectively); however, all control subjects in the analysis reached their reference date.

A total of 41.6% of the study population reported any history of smoking before the reference date, and 31.0% reported current smoking at the reference date. Data on smoking by study group are presented in Table 2. Among irradiated subjects, a higher frequency of ever smoking was observed in case patients, compared with control subjects ($P = .11$), whereas comparison of the nonirradiated case patients and control subjects showed a higher frequency of smoking among control

Table 1. Demographic characteristics of the study population by group

Characteristic	Irradiated subjects		Nonirradiated subjects	
	Case patients ($n = 160$)	Control subjects ($n = 145$)	Case patients ($n = 82$)	Control subjects ($n = 135$)
Age at diagnosis[a]				
Mean $\pm$ SD	45.9 $\pm$ 8.4	NA	48.5 $\pm$ 9.6	NA
Range	20-69		20-65	
Age at interview				
Mean $\pm$ SD	55.5 $\pm$ 5.6	54.7 $\pm$ 4.3	60.0 $\pm$ 6.9	56.1 $\pm$ 5.5
Range	45-73	46-66	45-74	46-74
Sex, no. (%) of subjects				
Male	52 (32.5)	43 (29.7)	19 (23.2)	41 (30.4)
Female	108 (67.5)	102 (70.3)	63 (76.8)	94 (69.6)
Origin, no. (%) of subjects				
Asia	66 (41.3)	63 (43.5)	41 (50.0)	57 (42.2)
Africa	83 (51.9)	82 (56.5)	31 (37.8)	70 (51.9)
Europe	11 (6.8)	0	10 (12.2)	8 (5.9)

NA indicates not available. SD indicates standard deviation.
[a]$P < .01$ for irradiated versus nonirradiated case patients.

Table 2. Distribution of smoking by study group

Characteristic	Irradiated subjects			Nonirradiated subjects		
	Case patients ($n = 160$)	Control subjects ($n = 145$)	*P*	Case patients ($n = 82$)	Control subjects ($n = 135$)	*P*
Ever smoking (yes), no. (%) of subjects	76 (47.5)	54 (37.2)	.11	27 (32.9)	60 (44.4)	.09
Current smoking (yes), no. (%) of subjects	58 (36.3)	41 (28.3)	.14	18 (22.2)	45 (33.3)	.10
Years since cessation						
Mean ± SD	11.2 + 11.6	11.0 + 5.6	[a]	11.1 + 9.8	15.9 + 8.6	[a]
Range	1-44	1-20		2-31	1-31	
Years since 1st use			[a]			[a]
Mean ± SD	22.6 + 9.6	20.0 + 8.8		23.9 + 11.5	23.3 + 8.8	
Range	3-46	1-43		3-45	1-39	
Age started smoking			.15			
Mean ± SD	21.1 + 5.8	22.8 + 7.1		22.9 + 7.3	22.6 + 6.4	[a]
Range	13-44	12-49		16-42	15-44	
Smoking pack-years			[a]			[a]
Mean ± SD	18.8 + 13.0	16.2 + 16.8		20.5 + 16.4	21.0 + 20.1	
Range	0.4-62.0	0.2-88.5		0.6-62.0	0.75-99.8	
No. (%) of subjects						
< 10	20 (27.0)	24 (45.3)		10 (37.0)	20 (37.0)	
10-20	25 (33.8)	16 (30.2)	.058	3 (11.1)	12 (22.2)	[a]
> 20	29 (39.2)	13 (24.5)		14 (51.9)	22 (40.7)	
Unknown	2	1		0	6	

SD indicates standard deviation.
[a] $P > 0.25$

subjects ($P = .09$). For past smokers, the number of years from cessation to reference date ranged between 1 to 44 years (mean ± SD,12.4 ± 9.3 years), with no differences between the groups. The number of years since first use of cigarettes ranged from 1-46 years (mean ± SD, 22.3 + 9.5 years), whereas the mean age (±SD) at smoking initiation was 22.2 + 6.5 years (range, 12-49 years). No differences between the groups were noted for these variables. Among both irradiated and nonirradiated subjects, the control subjects tended to be lighter smokers than the case patients, whereas subjects in both nonirradiated groups were heavier smokers than the irradiated subjects.

Table 3 shows ORs and 95% CIs for the association between smoking and meningioma. Overall, no association between smoking and meningioma was shown (OR, 1.08; 95% CI, 0.75-1.56 adjusted for radiation exposure). Although the overall OR for smoking among women was 0.79 (95% CI, 0.50-1.24), a significantly increased risk was observed in men who ever smoked (OR, 2.13; 95% CI, 1.09-4.15). The risk in men increased with increasing smoking pack-years from 1.67 for < 10 pack-years to 2.69 for > 20 pack-years (P for trend = .01). The increased risk in men who had ever smoked was consistent but not significant in both irradiated and non-irradiated male groups.

Among women, significant differences in the effect of smoking between irradiated and nonirradiated subjects were observed ($P < .01$ for the interaction between radiation and smoking). A significant protective effect was observed for smokers among the nonirradiated women (OR, 0.32; 95% CI, 0.14-0.77), with a significant negative dose-response association (P for trend < .01). Although for the lowest category of use (no. of pack-years, <10) a protective effect of ~ 50% was shown, for women who were heavy smokers (no. of pack-years, >20), the protective effect was ~ 90% compared with those who had never been smokers. Among irradiated women, although no association for the ever versus never category was found, heavy users showed a significantly increased risk.

Discussion

Our results suggest that smoking plays a role in the development of meningioma. However, this association differs between men and women and, in the latter group, is modified by irradiation. In this study, we found a significantly increased risk for meningioma among men who had ever smoked versus those who were never smokers, supported by a dose-response association. A different effect was found in women, in whom an interaction between radiation and smoking was observed. In the subgroup of nonirradiated women, smoking was associated with a significant protective effect for meningioma, with a strong dose-response association; among

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between active smoking and meningioma by sex, radiation status, and dose.

Total group	Total (main effect)				Irradiated subjects				Nonirradiated subjects			
	No. (%) of case patients	No. (%) of control subjects	OR[a]	(95% CI)	No. (%) of case patients	No. (%) of control subjects	OR	(95% CI)	No. (%) of case patients	No. (%) of control subjects	OR	(95% CI)
Never ($n = 305$)	139 (26.3)	166 (31.8)	1		84 (27.5)	91 (29.8)	1		55 (25.3)	75 (34.6)	1	
Ever ($n = 217$)	103 (19.7)	114 (21.8)	1.08	(0.75-1.56)	76 (24.9)	54 (17.7)	1.46	(0.92-2.33)	27 (12.4)	60 (27.6)	0.55	(0.28-1.10)
pkyrs[b] < 10	30 (10.6)	44 (15.6)	0.76	(0.44-1.33)	20 (15.7)	24 (18.9)	0.81	(0.39-1.67)	10 (12.3)	20 (24.7)	0.63	(0.26-1.51)
$10 \leq$ *pkyrs* ≤ 20	28 (9.9)	28 (9.9)	1.14	(0.64-2.05)	25 (19.7)	16 (12.6)	1.56	(0.77-3.14)	3 (3.7)	12 (14.8)	0.33	(0.08-1.31)
pkyrs >20	43 (15.2)	35 (12.4)	1.51	(0.89-2.55)	29 (22.8)	13 (10.2)	2.09	(1.00-4.38)	14 (17.3)	22 (27.2)	0.71	(0.27-1.82)
P for trend			.05				.04				.29	
Men												
Never ($n = 56$)	18 (11.6)	38 (24.5)	1		14 (14.7)	21 (22.1)	1		4 (6.7)	17 (28.3)	1	
Ever ($n = 99$)	53 (34.2)	46 (29.7)	2.13	(1.09-4.15)	38 (40)	22 (23.2)	1.9	(0.89-4.06)	15 (25)	24 (40)	3.35	(0.61-18.3)
pkyrs <10	12 (12.8)	12 (12.8)	1.67	(0.55-5.14)	9 (15.3)	7 (11.9)	1.79	(0.45-7.16)	3 (8.6)	5 (14.3)	2.27	(0.31-17.0)
$10 \leq$ *pkyrs* ≤ 20	13 (13.8)	13 (13.8)	1.64	(0.62-4.33)	13 (22)	6 (10.2)	2.35	(0.72-7.70)	0	7 (20)	<0.01	[c]
pkyrs >20	27 (28.7)	17 (18.1)	2.69	(1.21-5.98)	15 (25.4)	9 (15.3)	1.63	(0.66-4.01)	12 (34.3)	8 (22.9)	9.64	(0.97-95.6)
P for trend			.01				.19				.02	
Women[d]												
Never ($n = 249$)	121 (33)	128 (34.9)	1		70 (33.3)	70 (33.3)	1		51 (32.5)	58 (36.9)	1	
Ever ($n = 118$)	50 (13.6)	68 (18.5)	0.79	(0.50-1.24)	38 (18.1)	32 (15.2)	1.23	(0.68-2.23)	12 (7.6)	36 (22.9)	0.32	(0.14-0.77)
pkyrs <10	18 (15.8)	32 (28.1)	0.62	(0.32-1.20)	11 (16.2)	17 (25)	0.61	(0.25-1.49)	7 (15.2)	15 (32.6)	0.51	(0.18-1.45)
$10 \leq$ *pkyrs* ≤ 20	15 (13.2)	15 (13.2)	1.03	(0.48-2.18)	12 (17.6)	10 (14.7)	1.30	(0.53-3.16)	3 (6.5)	5 (10.9)	0.40	(0.07-2.40)
pkyrs >20	16 (14)	18 (15.8)	0.89	(0.42-1.90)	14 (20.6)	4 (5.9)	4.62	(1.01-21.24)	2 (4.3)	14 (30.4)	0.08	(0.01-0.67)
P for trend			.42				.10				$<.01$	

[a] Adjusted for radiation.
[b] *pkyrs* indicates pack-years (data available for 208 subjects [94 men and 114 women]).
[c] Very few cases in this category.
[d] $P < .01$ for interaction (radiation and smoking).

irradiated women, a nonsignificant increased risk was observed.

To the best of our knowledge, the association between smoking and meningiomas has been assessed in 9 case-control studies and 1 cohort study, the results of which were inconsistent.[8-17] Most of the studies found no statistically significant association between smoking and risk of meningioma, although 1 reported an increased risk and 2 studies reported a decrease in risk among women. In a study conducted in Australia, the investigators reported a nonsignificant OR of 1.77 (95% CI, 0.80-3.92) for ever versus never smoking cigarettes.[11] This report was based on only 12 male and 48 female patients with meningioma (211 and 206 control subjects, respectively); therefore, separate analyses of men and women were not conducted. In a study conducted in Los Angeles, which included 70 male patients and control subjects, the authors reported no remarkable differences between case patients and control subjects with regard to history of cigarette smoking (OR for ever versus never, 1.2; 95% CI, 0.6-2.7), age started smoking, amount smoked, years smoked, and pack-years of exposure.[14] These findings were in line with an earlier analysis of data on men in Los Angeles by the same investigator[13] and with a more recent study from Germany[15] that did not provide numerical data from the analysis of smoking but reported no significant difference between the smoking habits in male or female patients with meningioma versus control subjects. An additional study conducted in Germany reported relative risks for meningioma of 1.0 (95% CI, 0.5-2.0) and 1.6 (95% CI, 0.7-3.4) for current and past smokers, respectively, in a sample that included 21 male and 60 female case patients.[16] Furthermore, a recent cohort study of 1.3 million middle-aged women, of whom 390 developed meningioma over a mean follow-up period of 6.2 years, presented relative risks of 0.88 (95% CI, 0.66-1.16) and 0.86 (95% CI, 0.67-1.10) for developing meningioma for current and past smokers, respectively.[17] In contrast, in a study that was conducted in China, cigarette smoking was positively associated with meningioma risk in women but not in men. In women, compared with nonsmokers, the adjusted OR for pack-years of smoking above the median was 6.2 (95% CI, 2.04-18.87).[8]

Our findings are compatible with the results of a population-based case-control study conducted by Phillips et al,[9] who reported an increased risk for meningioma in men (OR, 2.1; 95% CI, 1.1-4.2) and a protective effect among women (OR, 0.7; 95% CI, 0.5-1.1). The study population included 143 female and 57 male case patients, with 2 control subjects matched to each case patient by age and sex. Among men, the risk increased with increasing numbers of cigarettes smoked daily, whereas among women the trend was the opposite. It is important to mention that the latter study evaluated smoking habits that occurred ≥ 10 or more years before meningioma surgery. A protective effect of smoking in women was also described in an analysis of the association between meningioma and reproductive factors, which included 219 female case patients and 260 control subjects. ORs of 0.6 (95% CI, 0.4-0.9), 0.5 (95% CI, 0.3-0.8), and 0.7 (95% CI, 0.5-1.1) were reported for ever, current, and past smokers, respectively. Stratification by menopausal status showed statistically significant protective effects for both current and past smokers who were premenopausal. However, the protective effect of current smoking did not reach statistical significance in postmenopausal women, and past smoking was associated with an OR of 1.2 (95% CI, 0.6-2.3) in this subgroup. The authors suggested that selected endogenous hormonal factors might play a role in limiting—rather than promoting—meningioma development, particularly among premenopausal women.[10]

Smoking is a potential risk factor for many cancer types as well as for many other diseases. Tobacco smoke contains and delivers > 4000 compounds; some are known carcinogens, such as benzyl (a) pyrenes and polycyclic aromatic compounds. In addition, the use of tobacco products is a major source of human exposure to various *N*-nitroso compounds. Dietary intake of *N*-nitroso compounds has been etiologically related to the development of adult and childhood brain tumors.[22,23]

The findings of a protective effect of smoking among nonirradiated women and an increased risk with increasing pack-years of smoking in irradiated women needs further elucidation. The observation of a protective effect in women in general (nonirradiated) is in accordance with the findings of Phillips et al[9] and of Lee et al.[10] Moreover, the significant dose-response relationship found in these studies supports a causal interpretation.

Several lines of evidence suggest that estrogen is associated with meningioma development, including the female predominance of the tumor,[24] the existence of estrogen (and progesterone) receptors on meningioma tumors,[25,26] and the reported association between breast cancer and meningiomas, as a second primary tumor.[27] Examination of the literature for other known hormonal-dependent neoplasms shows that smoking has been consistently associated with a decreased risk in endometrial cancer,[28]whereas breast cancer studies have variably shown positive, inverse, or null associations with smoking.[29] Cigarette smoking has been hypothesized to lower the risk of endometrial and breast cancer through antiestrogenic mechanisms. Smoking enhances the metabolism of estradiol to inactive cathechol estrogens and is associated with several other mechanisms, including increased binding of estrogens by serum sex-hormone-binding globulin and lowered levels of estrogen derived from adipose tissue.[30] Supporting this hypothesis are studies that have shown that smoking is associated with increased risk of osteoporosis (known to be related to low estrogen levels) and attenuated effects of hormone replacement therapy among smokers.[31]

Therefore, the sex-specific protective effect of smoking might be biologically plausible. We might speculate that the antiestrogenic effect of cigarette smoking is a possible biological mechanism that

reduces the risk for meningiomas among ever–smoking, nonirradiated women. However, it seems that for the irradiated women, other mechanisms act to create a different effect. Although exploring the exact mechanism for the different effects of smoking in the irradiated versus nonirradiated female groups is beyond the scope of this study, we suggest 3 possible explanations for the interaction seen. First, irradiated subjects who developed meningioma might represent a subgroup of individuals who are more susceptible to DNA-damaging environmental factors. Susceptibility to genotoxic carcinogens may result from variations in the metabolism of carcinogens[32] and from variations in the ability of individuals to repair carcinogen-induced DNA damage.[33] We have recently demonstrated clusters of familial meningiomas in irradiated siblings supporting the role of genetic susceptibility in the development of radiation-induced tumors.[34] We could assume that our irradiated case patients represent a genetically susceptible subpopulation that is less able to cope with DNA damage as a result of decreased repair capacity. This susceptible population might also be more vulnerable to the carcinogenic effect of smoking.

Another possible explanation could be that irradiated tumors are not estrogen sensitive. In that case, the estrogen antagonistic effect of smoking described above will not have a protective effect, and a possible oncogenic effect of smoking will prevail in these tumors.

The third possible explanation could be related to the mechanism of tumor development. The observed association with smoking seen in our study might be related to promotion—rather than initiation—of the tumor. Because our irradiated population was exposed to radiation in childhood and started to smoke in adulthood, it is reasonable to assume that radiation was the initiating factor, whereas smoking served as a promoting factor later in life. Thus, it might be that the initiator effect of radiation on the meninges, as well as a secondary effect on the vascular endothelium, is increased by the promoter effect of smoking on the already damaged vasculature. It is possible that the damaged vasculature increases the penetrance of carcinogens to the target cells.

Under these circumstances (increased genetic susceptibility or endothelial damage), even if cigarette smoking may have some antiestrogenic effects in women (and, thus, anticarcinogenic effects for meningiomas), these effects may be nullified or exceeded by the deleterious effects of smoking in irradiated women.

In summary, our study results demonstrate a significantly increased risk for meningiomas among men who ever smoked and a significant protective effect among nonirradiated women who ever smoked. To the best of our knowledge, our study group is the largest series of RAMs available in the literature. Moreover, our unique group of subjects with well-validated RAM, subjects with sporadic meningiomas, and 2 control groups of irradiated and nonirradiated individuals enables the examination of interaction between radiation and other candidate risk factors for meningioma. Existing epidemiological data are insufficient to determine causality for meningiomas with regard to smoking; however, our study results emphasize that the lack of concrete conclusions might be due to the varied and even inverse effects of this environmental factor by distinct host factors, such as past exposure to ionizing radiation and/or sex, which reflects hormonal factors.

Conflict of interest statement. None declared.

Funding

This research was partially funded by the Israel Cancer Association.

References

1. Modan B, Baidatz D, Mart H, Steinitz R, Levin SG. Radiation induced head and neck tumors. *Lancet*. 1974;1:277–279.
2. Ron E, Modan B, Boice JD, Jr., et al. Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med*. 1988;319:1033–1039.
3. Longstreth WT, Jr., Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. *Cancer*. 1993;72:639–648.
4. Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. *J Neurooncol*. 1996;29:197–205.
5. Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst*. 2002;94:1555–63.
6. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development following childhood exposure to ionizing radiation for tinea capitis. *Radiat Res*. 2005;163:424–432.
7. Centers for Disease Control and Prevention. *2004 Surgeon General's Report: The Health Consequences of Smoking*. Available at http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/00_pdfs/chapter2.pdf.
8. Hu J, Little J, Xu T, et al. Risk factors for meningioma in adults: a case-control study in northeast China. *Int J Cancer*. 1999;83:299–304.
9. Phillips LE, Longstreth WT, Koepsell T, Custer BS, Kukull WA, van Belle G. Active and passive cigarette smoking and risk of intracranial meningioma. *Neuroepidemiology*. 2005;24:117–122.
10. Lee E, Grutsch J, Persky V, Glick R, Mendes J, Davis F. Association of meningioma with reproductive factors. *Int J Cancer*. 2006;119:1152–1157.
11. Ryan P, Lee MW, North JB, McMichael AJ. Risk factors for tumors of the brain and meninges: Results from the Adelaide adult brain tumor study. *Int J Cancer*. 1992;51:20–27.
12. Preston-Martin S, Paganini-Hill A, Henderson BE, Pike MC, Wood C. Case-control study of intracranial meningiomas in women in Los Angeles County, California. *J Natl Cancer Inst*. 1980;65:67–73.

13. Preston-Martin S, Yu MC, Henderson BE, Roberts C. Risk factors for meningiomas in men in Los Angeles County. *J Natl Cancer Inst*. 1983;70:863–866.
14. Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res*. 1989;49:6137–6143.
15. Schneider B, Pulhorn H, Rohrig B, Rainov N. Predisposing conditions and risk factors for development of symptomatic meningioma in adults. *Cancer Detect Prev*. 2005;29:440–447.
16. Schlehofer B, Kunze S, Sachsenheimer W, Blettner M, Niehoff D, Wahrendor J. Occupational risk factors for brain tumors: results from a population-based case-control study in Germany. *Cancer Causes Control*. 1990;1:209–215.
17. Benson VS, Pirie K, Green J, Casabonne D, Beral V for the Million Women Study Collaborators . Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *Br J Cancer*. 2008;99:185–190.
18. Sadetzki S, Modan B. Epidemiology as a basis for legislation: how far should epidemiology go?. *Lancet*. 1999;353:2238–39.
19. Sadetzki S, Modan B, Chetrit A, Freedman L. An iatrogenic epidemic of benign meningioma. *Am J Epidemiol*. 2000;151:266–272.
20. Werner A, Modan B, Davidoff D. Doses to brain, skull, and thyroid, following X-ray therapy for tinea capitis. *Phys Med Biol*. 1968;13:247–258.
21. S-Plus 2000 Professional Release 3. Seattle: MathSoft, Inc., 2000.
22. Giles GG. What do we know about risk factors for glioma? *Cancer Causes Control*. 1997;8:3–4.
23. Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Preston-Martin S. A review: dietary and endogenously formed N-nitroso compound and risk of childhood brain tumors. *Cancer Causes Control*. 2005; 16:619–635.
24. CBTRUS (2002). *Statistical Report: Primary Brain Tumors in the United States, 1995–1999*. Published by the Central Brain Tumor Registry of the United States. Available at http://www.cbtrus.org/reports/202/2002report.pdf
25. Carroll RS, Zhang J, Black PM. Expression of estrogen receptors alpha and beta in human meningiomas. *J Neurooncol*. 1999;42:109–116.
26. Blankenstein MA, Koehorst SGA, van der Kallen CJH, et al. Oestrogen receptor independent expression of progestin receptors in human meningioma–a review. *J Steroid Biochem Molec Biol*. 1995;53:361–365.
27. Lieu AS, Hwang SL, Howng SL. Intracranial meningioma and breast cancer. *J Clin Neurosci*. 2003;10:553–556.
28. Terry PD, Rohan TE, Franceschi S, Weiderpass E. Cigarette smoking and the risk of endometrial cancer. *Lancet Oncol*. 2002;3:470–480.
29. Terry PD, Rohan TE. Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2002;11:953–971.
30. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. *Am J Obstet Gynecol*. 1990;162:502–514.
31. Tanko LB, Christiansen C. An update on the antiestrogenic effect of smoking: a literature review with implications for researchers and practitioners. *Menopause*. 2004;11:104–109.
32. Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*. 1997;6:733–743.
33. Berwick M, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. *J Natl Cancer Inst*. 2000;92:874–897.
34. Flint-Richter P, Sadetzki S. Genetic predisposition for the development of radiation-assoicated meningioma: an epidemiological study. *Lancet Oncology*. 2007;8:403–410.