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ORIGINAL PAPER

Secondary cancer after meningioma diagnosis: an Israeli national study

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Abstract

Background There are limited data on whether primary diagnosis of meningioma may be associated with development of secondary primary cancer (SPC).

Methods All meningioma cases (ICD-O-3 morphology codes 9530/0–9539/3) diagnosed in Jewish Israelis ≥ 20 years 1990 through 2015 registered in the Israel National Cancer Registry (INCR) were retrieved. All subsequent cancers occurring more than 6 months after meningioma diagnosis were identified. Risk of secondary cancer (SPC) was compared to cancer risk in the general population through the calculation of standardized incidence ratios (SIRs) and excess absolute risks (EARs). SIRs were stratified by type of second cancer, sex, and age group. Cox regression models were used to estimate hazard ratios of developing SPC.

Results Overall, 8044 meningioma cases were identified: mean age at diagnosis was 64.0 ± 14.1 years. Of these, 927 (11.5%) were diagnosed with SPC (SIR 1.6, 95% CI 1.5–1.7). SPC risk was elevated in men (SIR 1.6, 95% CI 1.5–1.9) and women (SIR 1.6, 95% CI 1.5–1.8) diagnosed with meningioma in univariable analyses. Cancers most commonly encountered in the studied population were breast (17.6%), colorectal (13.4%), lung (8.1%), prostate (5%), and bladder (4.6%) cancer. In multivariable analyses, 10+ year increment in age at meningioma diagnosis was significantly associated with higher risk for SPC in individuals diagnosed with meningioma between 20 and 64 years, with an inverse association in the older age group (65+ years).

Conclusions Meningioma diagnosis is associated with an increased risk for developing secondary cancers. This risk should be discussed with patients treated for meningioma.

Keywords Meningioma · Secondary primary cancer · Early detection · Risk factors

Introduction

Meningiomas are the most common benign tumors of the central nervous system (CNS) with an age-adjusted incidence rate (per 100,000 person/years) of 8.36 and 3.61 for females and males, respectively, and a population prevalence rate of 97.5/100,000 in the United States [1]. Meningiomas most commonly occur sporadically with no discernable family history, and are not associated with additional neoplasms or inherited tumor predisposition syndromes, except for over-representation of meningiomas in cases with Neurofibromatosis type 2 (NF2) [2]. Exposure to ionizing radiation, in particular therapeutic irradiation for childhood cancer [3], and in atomic bomb survivors [4], is a well- established risk factor for meningioma. Several studies have suggested radiotherapy and chemotherapy administered for the treatment of pediatric cancer confer an increased risk of meningioma

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[3, 5], with an estimated 1 in 8 childhood cancer survivors developed late meningioma by age 40 years, correlated with radiation dose and exposure age [3].

Studies that have focused on secondary primary cancers (SPCs) diagnosed in patients initially diagnosed with meningioma have yielded inconsistent results. Some studies reported no statistically significant risk for developing breast cancer [6, 7] or any cancer type studied [8–10] regardless of meningioma irradiation treatment [8, 9] and malignant meningioma phenotype [8, 10]. Taken together, these studies indicate no increased risk for SPCs in persons diagnosed with malignant meningioma compared with the risk of primary cancer in the general population.

In contrast to the above-referenced studies showing no excess risk for secondary cancer after meningioma diagnosis, Davis et al. [11] evaluated the risk of SPCs after meningioma diagnosis in Sweden between 1958 and1997. Of 12,012 meningioma cases, 926 (7.7%) were diagnosed with any SPC, with SIR = 1.2 (95% CI 1.1–1.3). Specifically, statistically significant SIRs were observed for renal cancer (SIR = 1.6), melanoma (SIR = 1.7), thyroid cancer (SIR = 2.6), and brain tumors (SIR = 2.6). The long-term prognosis and quality of life of meningioma patients are undoubtedly influenced by long-term morbidity that may be associated with the treatment they received for their primary cancer, and more data are needed in this respect. In the present study, data from the Israel National Cancer Registry were used to calculate the risk of subsequent cancer diagnoses in individuals diagnosed with meningioma during the period from 1990 to 2015.

Methods

Patients

Cancer Registry-The Israel National Cancer Registry (INCR), established in 1960, is a population-based, passive, national registry covering the population of the State of Israel (approximately 9 million in 2020). The registry records all incident cases of in situ and malignant neoplasms (with the exception of squamous cell and basal cell carcinomas of the skin), and benign neoplasms of the brain and central nervous system. Reporting to the registry has been mandatory since 1982. The completeness of the INCR's data has been estimated at 97% for solid tumors and 87% for hematopoietic tumors [12].

All cases registered in the INCR database meeting the following criteria were identified: diagnosis of meningioma (ICD-O-3 morphology codes 9530/0–9539/3) during the period from 1990 to2015; age 20 and over at the time of the meningioma diagnosis; no history of malignant disease prior to the meningioma diagnosis; date of diagnosis of meningioma not equal to the date of death; meningioma diagnosis not based solely on a death certificate; Jewish religion, as recorded in the National Population Registry. Persons of other ethnicities were excluded from analysis as they comprised only 10% of the population of meningioma patients.

For all persons meeting the study inclusion criteria, we searched the registry database for subsequent cancer diagnoses. Individuals diagnosed with a second primary cancer (SPC) less than 6 months after the index meningioma diagnosis were excluded from the study cohort, in order to avoid including primary cancers that may have been present, but not clinically evident, at the time of the meningioma diagnosis. Follow-up time was calculated as time from meningioma diagnosis to the first of the following events: (1) SPC diagnosis, (2) death, (3) the end of the follow-up period (31 December 2017). The study was approved by the Sheba Medical Center ethics committee.

Statistical analyses

We conducted a descriptive analysis of the meningioma cohort with attention to covariates likely to be associated with the development of a second primary malignancy [age at meningioma diagnosis, sex, tumor behavior of meningioma (invasive/noninvasive), and year of meningioma diagnosis].

The outcome of interest was the diagnosis of any SPC after a prior diagnosis of meningioma. Age at meningioma diagnosis was grouped into two age groups: 20–64 years, and 65+ years. The reason for this age-based subdivision was an attempt to highlight the putative effects of genetic predisposition to tumor development (presumably more apparent in the younger age group). We calculated the rate of SPC as the number of persons diagnosed with a subsequent primary cancer divided by total person-years of follow-up.

Cumulative incidence of second primary cancers

The Kaplan–Meier method was used to estimate the cumulative incidence of SPC in persons with meningioma during the period of follow-up, stratified by age at meningioma diagnosis and sex group. Gray's test was used to test the homogeneity of cumulative incidence functions (CIF) between age and sex groups.

Calculation of standardized incidence ratios and excess absolute risks

We calculated standardized incidence ratios (SIR) for all subsequent SPC and for the most frequently occurring cancer types as the number of cases observed in the study cohort during the follow-up period, divided by the number

of cases that would be expected in the cohort on the basis of age, sex, and population-group specific cancer rates for the Israeli Jewish population [13]. We calculated excess absolute risks as the difference between the number of observed and expected events divided by the number of person-years in follow-up and expressed per 100,000.

Risk factor analysis

We used multivariable Fine and Gray's proportional subdistribution hazard models (PSH) to examine the risk of developing SPC following meningioma diagnosis in each of the age groups defined, adjusting for age at meningioma diagnosis as a continuous variable, using increments of 5, 10, and 20 years, as well as adjusting for sex and year of meningioma diagnosis, and considering death as a competing risk.

Hazard ratios were generated for SPC risk at 5, 10, and 15 years after meningioma diagnosis. Standard asymptotic inference methods for COX regression that were based on partial likelihood were used to construct 95% confidence intervals and to carry out two-sided tests of statistical significance. All reported p values were two-sided and considered statistically significant if < 0.05.

Results

Overall, the study encompassed 8,044 meningioma cases [140 (1.7%) malignant] who met the study inclusion criteria, with a total of 40,134 person-years in follow-up (Fig. 1) (median follow-up 4.5 years, interquartile range 2.4 to 6.7 years). Of these cases, 2,308 (28.7%) were males, and 5,736 (71.3%) females. Mean age at diagnosis was 64.1 years (Standard Deviation, SD = 13.5) and 63.8 years (SD = 14.4), for males and females, respectively. Overall, 927 (rate of 15.7 per 1000 person-years) of participants were diagnosed with SPCs during follow-up (Table 1). Almost 50% of SPC were diagnosed 1 to 5 years following meningioma diagnosis, and an additional 25% were diagnosed 5 to 10 years following that diagnosis.

Standardized incidence ratio and excess absolute risk analysis

The five most common SPC in males were prostate (16.8%), colorectal cancer (15.0%), lung cancer (11.3%), bladder cancer (10.0%), and non-Hodgkin lymphoma (6.3%). In females, breast cancer (25.0%), colorectal cancer (12.7%),

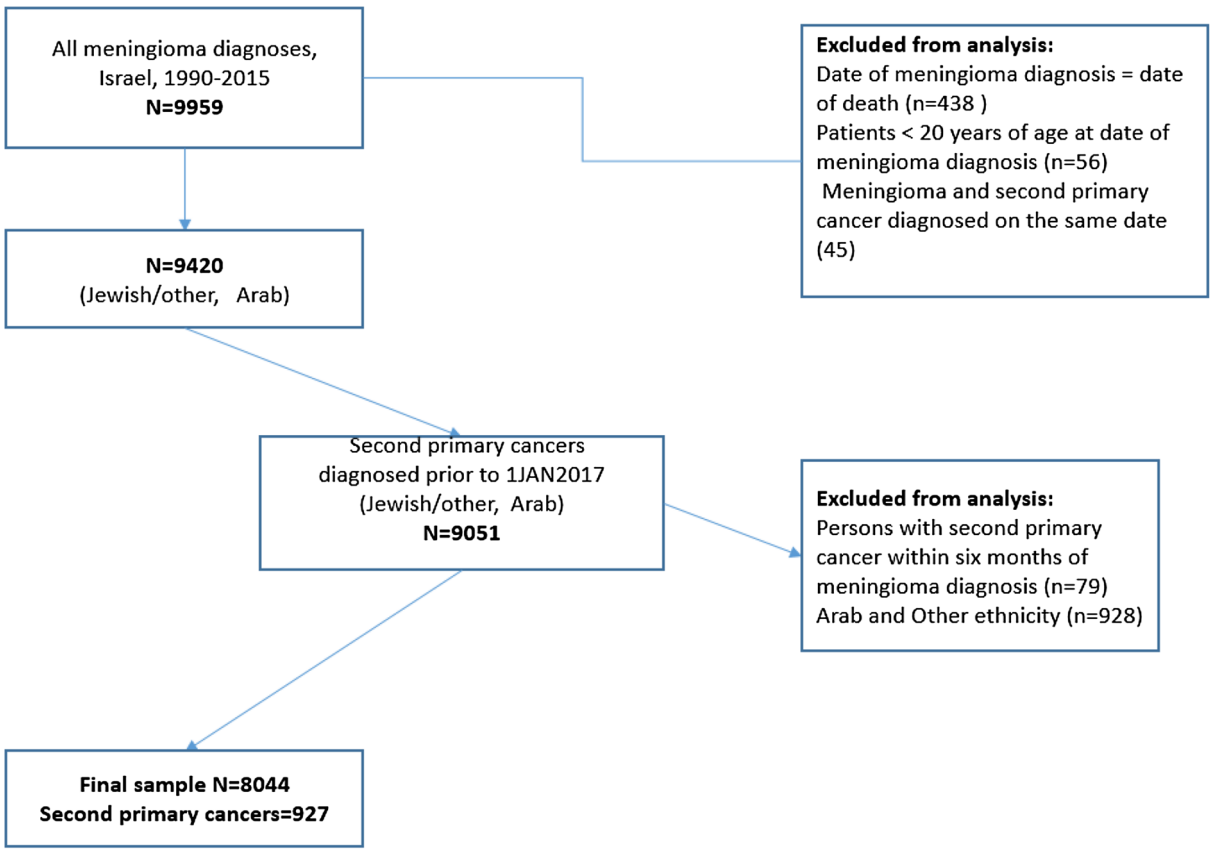

Fig. 1 Selection of study subjects

Table 1 Demographics and clinical characteristics of study subjects

	No SPC (%) $n=7,117$	SPC (%) $n=927$	p value
Type of meningioma			
Non-malignant	6989 (98.0)	915 (99.0)	0.3484
Malignant	128 (2.0)	12 (1.0)	
Diagnosis period			
1990–2009	5193 (73.0)	835 (90.0)	< 0.0001
2010–2015	1924 (27.0)	92 (10.0)	
Gender			
Male	2033 (28.6)	275 (29.7)	0.4873
Female	5084 (71.4)	652 (70.3)	
Age group at meningioma diagnosis			
20–64	3833 (53.9)	284 (30.6)	< 0.0001
65+	3284 (46.1)	643 (69.4)	

lung cancer (6.9%), thyroid cancer (4.3%) and cancer of the uterus (4.2%) were the most commonly encountered SPCs. Both men and women with a meningioma diagnosis had an elevated risk of developing a SPC compared with the general population (SIR 1.6, 95% CI 1.5–1.9 and 1.6, 95% CI 1.5–1.8, respectively) (Table 2). In males, the SIR was statistically significant for most cancer types with the notable exception of pancreatic cancer, gastric cancer, malignant melanoma, stomach cancer and thyroid cancer (Table 2). In females, the risks of SPC for all cancer types analyzed were statistically significant with the exception of bladder and non-Hodgkin lymphoma (Table 2).

Cumulative incidence rates

We analyzed the cumulative incidence rates for developing SPC. We compared the cumulative incidence function (CIF) between age groups by using Gray's test, as presented in Fig. 2. We found that the cumulative incidence rate for SPC at 20 years after first meningioma diagnosis was higher among persons who were older at the time of meningioma diagnosis: 9.9% (95% CI 8.79–11.27%) among 20–64 year olds and 23.76% (95% CI 22–29.4%) among those 65 and older age. We found no association between sex and cumulative risk of SPC ($p=0.7207$).

Risk factor analysis

We used multivariable Fine and Gray's proportional subdistribution hazard models (PSH) to examine the risk of developing SPC following meningioma diagnosis. The proportional hazard assumption for age effect was violated, since the effect of age varies over time; therefore, the final Cox regression model was fitted accordingly: analysis by age groups (20–64 years and 65+ years), adjusting for age at meningioma diagnosis as a continuous variable (using increments of 5, 10 and 20 years), sex, and year of meningioma diagnosis categorized into two time periods (1990–2009 and 2010–2015) and considering death as a competing risk. Interaction between age and time of diagnosis was significant; however, this was not included in the final model due to its negligible effect. This model showed significant independent association of age with risk of developing SPC. Individuals diagnosed with meningioma in the younger age group (20–64 years), increments of 10 and 20 years in age at diagnosis were significantly associated with higher risk for SPC: HR 1.66 (95% CI 1.02–2.72) and HR 4.25 (95% CI 2.38–7.60), respectively. In persons diagnosed with meningioma in the older age group (65+ years), increments of 5, 10, and 20 years in age at diagnosis were significantly associated with lower risk for SPC: HR 0.72 (95% CI 0.53–0.97), HR 0.71 (0.52–0.96) and HR 0.69 (95% CI 0.49–0.97), respectively (Table 3).

Discussion

The current study shows that a history of meningioma, in most cases a benign tumor, increases the risk for developing a host of secondary cancers, more often in individuals older than 65 years of age at the time of meningioma diagnosis. However, while in individuals diagnosed with meningioma between 20 and 64 years of age a more advanced age at meningioma diagnosis is a significant risk factor for SPC, this association is inverse in the older age group (65+ at meningioma diagnosis). Diagnosis of more than one tumor type in a single individual is one of the hallmarks of cancer susceptibility [14]. Yet, cancer susceptibility syndromes that encompass meningioma risk are rare, and primarily include Neurofibromatosis type 2 (NF2) [15]. While it is still possible that a subset of cases analyzed herein are indeed unrecognized NF2 cases, the spectrum of malignant tumors that are encountered in these unselected meningioma cases far exceeds those associated with NF2 (acoustic neuroma, for the most part). Moreover, given the estimated rates of NF2 (1–9/100,000) [16] it is unlikely that NF2-enriched cases underlie the observed increased cancer rates.

While there is ample evidence regarding the association between therapeutic irradiation for a malignant tumor and the subsequent development of meningioma [17], there are few reports of a meningioma association with subsequent cancer. Helseth et al. [6] reviewed the association between meningioma and breast cancer in Norway from 1955 to 1986, and reported that the relative risk (RR) for developing breast cancer in women aged 50–64 years who were initially diagnosed with meningioma and followed up for 3,932 person/years was significantly elevated (RR 1.92 CI 1.02–3.29). Risk for renal cancer in men was also elevated

Table 2 Cancer types and SIR of second primary cancers by site of second primary cancer and gender

		Observed	Expected	SIR (95% CI)	EAR
All reportable diagnoses	All	927	583	1.6 (1.5–1.7)	857.4
	Male	275	167	1.6 (1.5–1.9)	1015.1
	Female	652	397	1.6 (1.5–1.8)	863.2
All invasive cancer	All	869	530	1.6 (1.5–1.8)	844.9
	Male	259	151	1.7 (1.5–1.9)	1010.4
	Female	610	362	1.7 (1.6–1.8)	842.2
Colorectal	All	124	71	1.8 (1.5–2.1)	133.1
	Male	41	20	2 (1.4–2.7)	194.6
	Female	83	47	1.8 (1.4–2.2)	121.0
Prostate	All	46	27	1.7 (1.2–2.2)	175.8
	Male	46	27	1.7 (1.2–2.2)	175.8
Breast (invasive)	All	163	100	1.6 (1.4–1.9)	212.6
	Female	163	100	1.6 (1.4–1.9)	212.6
Lung	All	76	57	1.3 (1.1–1.7)	48.3
	Male	31	20	1.6 (1.1–2.2)	105.3
	Female	45	31	1.5 (1.1–2)	49.2
Thyroid	All	34	9	3.6 (2.5–5.1)	61.5
	Male	5	2	2.7 (0.9–6.3)	30.1
	Female	29	8	3.4 (2.3–4.9)	69.8
Bladder	All	43	39	1.1 (0.8–1.5)	10.7
	Male	27	18	1.5 (1–2.1)	80.8
	Female	16	10	1.6 (0.9–2.6)	20.7
Non-Hodgkin lymphoma	All	42	29	1.4 (1–1.9)	31.6
	Male	17	8	2 (1.2–3.3)	80.8
	Female	25	20	1.3 (0.8–1.8)	17.0
Uterus	All	28	19	1.5 (1–2.1)	31.2
	Female	28	19	1.5 (1–2.1)	31.2
Kidney	All	33	16	2 (1.4–2.8)	41.1
	Male	14	6	2.2 (1.2–3.7)	72.4
	Female	19	8	2.5 (1.5–3.9)	38.7
Malignant brain/CNS	All	31	7	4.6 (3.1–6.6)	60.5
	Male	8	2	4 (1.7–7.9)	56.4
	Female	23	4	5.2 (3.3–7.8)	63.1
Pancreas	All	32	23	1.4 (0.9–1.9)	21.4
	Male	7	7	1 (0.4–2.1)	1.9
	Female	25	16	1.6 (1–2.4)	31.9
Stomach	All	22	18	1.3 (0.8–1.9)	11.0
	Male	10	6	1.6 (0.8–3)	35.7
	Female	12	9	1.3 (0.7–2.3)	9.2
Malignant melanoma	All	28	23	1.2 (0.8–1.8)	12.2
	Male	7	8	0.9 (0.4–1.9)	−6.6
	Female	21	13	1.6 (1–2.4)	26.4
Breast (in situ)	All	20	12	1.7 (1–2.6)	28.1

EAR excess absolute risk per 100,000

(RR 4.76 $p=0.05$). Claus et al. [18] reported that meningioma patients ($n=1{,}124$) were more likely than the controls ($n=1{,}000$) to have a family history of meningioma in a first-degree relative (OR 4.4, 95% CI 1.6–11.5), personal history of thyroid cancer (OR 4.7, 95% CI 1.02–21.5), or leukemia (OR 5.4, 95% CI 1.2–24.1) (most after radiotherapy). These are all indirect lines of evidence that support the notion of a common genetic predisposition to meningioma and SPC.

A common clinical practice in Israel in the 1950's to the early 1960's was to use low dose irradiation to treat Tinea

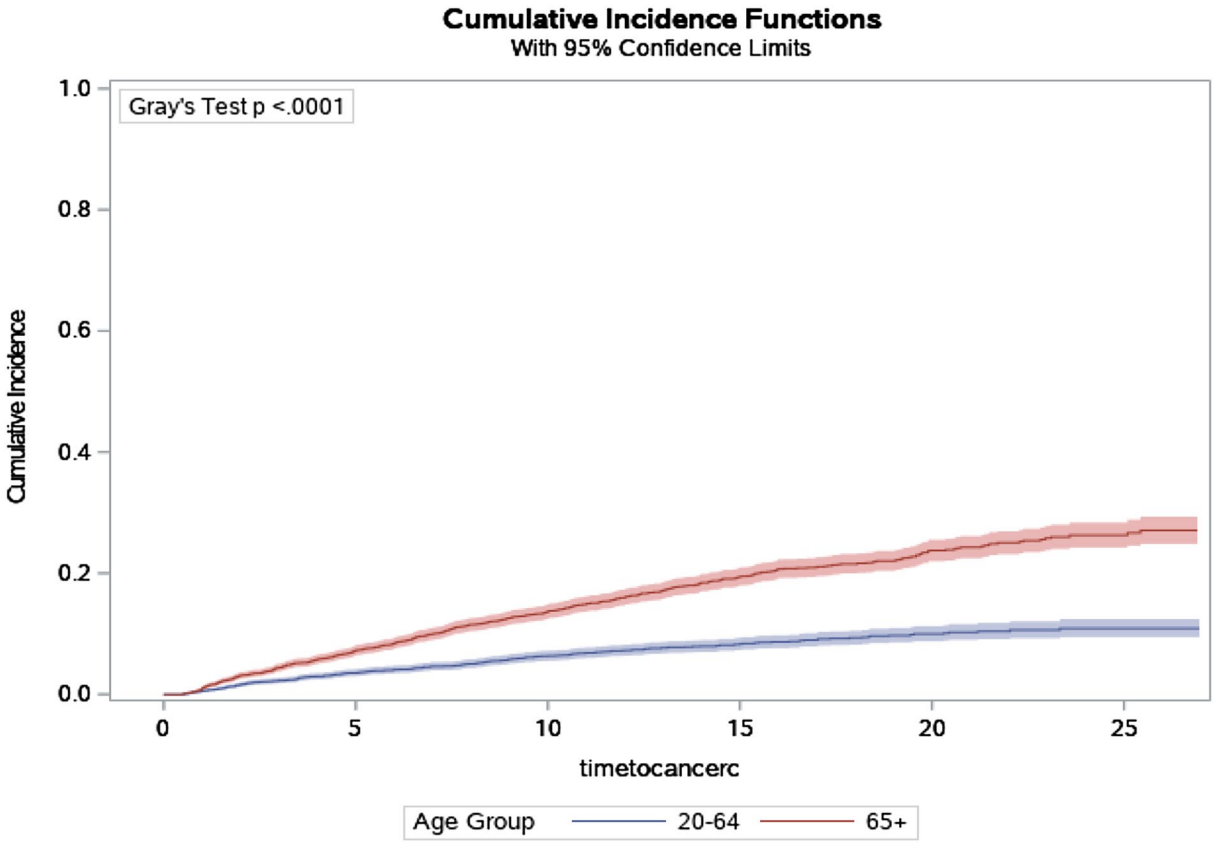

Fig. 2 Cumulative incidence curve of second primary cancer in persons diagnosed with meningioma, stratified by age group. (Color figure online)

Table 3 Cox multivariable regression models predicting overall occurrence of SPC after meningioma diagnosis with age as a continuous variable

Category	HR (95%)	*p* value
a. Age as a continuous variable in the young age group (20–64 years)		
Sex (female vs male)	0.91 (0.71–1.17)	0.4677
Period (2010–2015 vs. 1990–2009)	1.40 (0.93–2.10)	0.1075
5-Unit change in age	1.04 (0.65–1.68)	0.8662
10-Unit change in age at	1.66 (1.02–2.72)	0.0429
20-Unit change in age at diagnosis	4.25 (2.38–7.60)	< 0.0001
b. Age as a continuous variable in the old age group (65+ years)		
Sex (female vs. male)	1.10 (0.93–1.30)	0.2803
Period (2010–2015 vs. 1990–2009)	1.50 (0.49–0.97)	0.0324
5-Unit change in age	0.72 (0.53–0.97)	0.0307
10-Unit change in age at	0.71 (0.52–0.96)	0.0274
20-Unit change in age at diagnosis	0.69 (0.49–0.97)	0.0307

Capitis, especially in new immigrants from North Africa [19]. A subset of these irradiated individuals developed benign (and malignant) brain tumors. In the most comprehensive long-term follow-up (40-year-median follow-up) 67/10,834 irradiated individuals were diagnosed with meningiomas [20]. Thus, it seems that even if a small subset of the current cohort did undergo low dose irradiation for Tinea capitis, the overall effects on the results would be minimal.

One possible mechanism that may be considered to account for the meningioma-SPC association may be a yet unknown cancer susceptibility gene that confers higher susceptibility to SPC in a subset of meningioma cases. Supportive evidence for this possibility was reported by Hemminki et al. [21] who assessed the risk for first degree relatives of individuals with meningioma to develop the same tumor type. In that study, the standardized incidence ratios (SIRs) for familial risk were increased: when either of the parents was diagnosed with meningioma, the SIR for offspring was 3.06, and for an affected sibling, the SIR was 4.41. These increased familial risks may indicate a common genetic factor or a shared environmental exposure. Barchana and Liphshitz [22] reported that based on a limited number of benign meningioma cases ($n = 412$) Iranian Jews living in Israel have higher rates of meningioma compared with rates in other Jewish communities originating in Balkan states: 1.46-fold compared with Turkish Jews and 1.86-fold compared with Jews of Bulgarian, Greek origin. To further explore the possibility of genetic susceptibility, subsequent studies

should focus on families displaying this meningioma—SPC phenotype and combine whole exome/ whole-genome sequencing technologies to identify the putative gene(s). In addition, the surveillance scheme that meningioma cases are offered after diagnosis may account for higher rates of SPC diagnosis. Thus, cancers may have been incidentally diagnosed in meningioma cases who remain under medical surveillance after meningioma diagnosis. This possibility needs to be further explored, if the results of the current study are validated. Moreover, assessment of the impact of such a seemingly early stage cancer on survival can only be prospectively assessed.

Age-adjusted risk analysis showed that in individuals diagnosed with meningioma under 64 years of age the risk for SPC increased in those older at meningioma diagnosis whereas in those diagnosed with meningioma above that age, the association between age at meningioma diagnosis and SPC risk was inverse. Several factors could account for that difference. The small number of individuals diagnosed at the older age group, a survival bias for those who did get to age 65 and above, and the relatively shorter life span of the older vs. the younger age group.

The results of this preliminary study should be validated in larger, ethnically diverse, prospective studies. If validated, there may be clinical implications to the observed higher SPC risk. These increased risks, once quantified, should be discussed with meningioma cases by the treating physician and surveillance schemes should be evaluated to facilitate early detection of specific cancer types, whenever possible and cost effective.

The limitations of the current study should be considered. This is a single country experience and cancer susceptibility may be distinct in other ethnically diverse, genetically heterogeneous populations. The possibility of a selection bias should also be considered, as reporting of non-malignant cases may be non-complete and one of the caveats. Furthermore, meningioma diagnosis may either lead to increased medical surveillance, or mark a subgroup of individuals who are using the medical system more regularly and thus have their tumors detected sooner. Additionally, our inability to adjust for potential confounders, especially variables that are associated with both meningioma incidence and other cancers occurrence such as smoking and obesity, may have caused information bias. Specifically, given the fact that smoking status is missing from the majority of cases reported herein, and the known effect that smoking has on multiple cancer types, this is a major limitation.

In conclusion, a history of meningioma is associated with an increased risk for developing a variety of cancer types, especially in individuals aged 65 years of age and over at meningioma diagnosis. These results, if validated in subsequent studies, may have clinical implication and may offer early detection schemes tailored to these individuals.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval The Institutional Review Board of the Sheba Medical center approved the study.

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