RESEARCH ARTICLE

High Incidence of Benign Brain Meningiomas among Iranian-born Jews in Israel may be Linked to both Hereditary and Environmental Factors

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Abstract

Background: Following research demonstrating an increased risk for meningiomas in the Jewish population of Shiraz (Iran) we conducted a cohort analysis of meningiomas among Jews originating in Iran and residing in Israel. Materials and Methods: We use the population-based registry data of the Israeli National Cancer Registry (INCR) for the main analysis. All benign meningioma cases diagnosed in Israel from January 2000 to the end of 2009 were included. Patients that were born in Iran, Iraq, Turkey, Bulgaria and Greece were used for the analysis, whereby we calculated adjusted incidence rates per 100,000 people and computed standardized incidence ratios (SIRs) comparing the Iranian-born to each of the three other groups. Results: Iranian-born Jews had statistically significant higher meningioma rates rates compared to other Jews originating in Balkan states: 1.46 fold compared to Turkish Jews and 1.86 fold compared to the Bulgaria-Greece group. There was a small increase in risk for the Iranian born group compared to those who were born in Iraq (1.06, not significant). Conclusions: Higher rates of meningiomas were seen in Jews originating in Iran that are living in Israel as compared to rates in neighboring countries of origin. These differences can be in part attributed to early life environmental exposures in Iran but probably in larger amount are due to genetic and hereditary factors in a closed community like the Iranian Jews. Some support for this conclusion was also found in other published research.

Keywords: Meningioma - cancer epidemiology - Jews - Balkan states - Iranian

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Introduction

A recently published article demonstrated an increased risk for meningiomas in the Jewish population of Shiraz (Iran) and the author's stipulated that some genetic factors may be involved (Taghipour et al., 2010). This report used prevalence data and crude rates, which can not be directly compared, but in order to focus on the matted we conducted a cohort analysis of Meningiomas among Jews originating in Iran and residing in Israel using adjusted incidence rates of a population-based cancer registry.

Meningiomas (both malignant and benign) constitute the second most frequent group of brain tumors (after gliomas). In Israel there is a close monitoring after these tumors since the late Prof. Modan published his findings on the association between scalp irradiation for tinea capitis in the 50's of the previous century and the increase risk for brain tumors in general and meningiomas in particular (Modan et al., 1977; Ron et al., 1988; Ron et al., 1991). It should be emphasized that the research focused on Jews emigrating from North African countries that were the main group of people that was irradiated (Levin et al., 1995; Sadetzki et al., 2005).

The major risk factor for meningioma is, according current knowledge, exposure to ionizing radiations with risks from six fold to ten fold reported (Ron et al., 1991) including several studies reporting that patients having a full-mouth X-rays had a significantly increased risk of meningioma (Longstreth et al., 2004). Female Hormones use (either as oral contraceptives or hormone replacement therapy) showed conflicting results regarding the association with meningioma (Jhawar et al., 2003). Head trauma was another factor linked to meningioma, but results across studies are inconsistent (Preston-Martin et al., 1980; Inskip et al., 1998; Eskandary et al., 2005). Attempts to link specific chemicals with meningioma in occupationally or industrially exposed groups have proved inconclusive (Claus et al., 2005; Terry et al., 2009).

There are several known syndromes that are considered to be a predisposing factor for brain cancers. These include Li-Fraumeni syndrome, tuberous sclerosis, Turcot's syndrome and neurofibromatosis. An inherited germ-line mutation seems to be the underlying cause of this predisposition (Bell et al., 1999; Ruijs et al., 2010). Other conditions are probably caused by mutations in genes involved in DNA repair like in Turcot's syndrome

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(Hamilton et al., 1999). Brain tumors are often clustered within members of wide families and can be the result of both environmental and genetic factors (Offit et al., 2003; Malmer et al., 2009). Meningiomas are reported in families of several cancer predisposition syndromes including those involving the genes NF1, PTCH, CREBBP, VHL, PTEN, and CDKN2A (Simon et al., 2007). Another study conducted in Israel (Blumenthal, 2008) found a strong evidence for a familial contribution to primary brain cancer risk. There is evidence that this familial aspect includes not only shared environment, but also a heritable component. Other studies indicated common genetic polymorphisms in innate immunity genes that may be associated with risk of meningioma (Rajaraman et al., 2010) and that microsatellite instability found indicates that mismatch repair may also be targeted in meningioma (Pećina-Slaus et al., 2010). Molecular genetic findings have demonstrated that approximately half of meningiomas exhibit allelic loss. In addition, loss of heterozygosity on chromosome 22 is thought to be relevant to the tumorigenesis of meningioma (Seizinger et al., 1987; Kolles et al., 1995).

Along the history Jews tended to live a relatively segregated life and in particular when it came to marriage that were for the most within their communities. There are several known pathologies that are common in Jews (and with the further distinction of Ashkenazi and Sepharaditic branches). There are reports on BRCA mutations that were found and are more common among Ashkenazi Jewish women (Mandel'shtam et al., 2001). A particular changes in a single base in the T-A-T-A box was found in Jewish Kurds related to of Beta thalassemia (Poncz et al., 1982; Surrey et al., 1985) and evidence of genetic etiology in CJD disease among Jews originating in Libya with a vertical transmission in autosomal dominant inheritance with unknown penetrance (Gabizon et al., 1994). Another evidence of familial aggregation of disease in Jews was demonstrated regarding pulmonary alveolar proteinosis (PAP) with a high prevalence of PAP in Israeli Jews who had immigrated from North Africa or Iraq and a strong familial aggregation of the disease (Ben-Dov et al., 1999).

It seems that incidence rates of brain tumors in general and meningiomas in particular are relatively high among Middle Eastern populations and in Iran in particular (Alimohamadi et al., 2008; Nasseri et al., 2009). Few studies were conducted regarding Jewish population and Meningiomas. In a study conducted in the US from 1994-1998 it was found that Jews had a significantly 4 times fold higher rates compared to non-Jews (Inskip et al., 2003). Another study conducted in the US (Preston-Martin et al., 1989) found high rates of brain tumors in Jews residing in Los Angeles county and an increased incidence in Middle Eastern born populations in general.

The current study focuses on the question of a possible excess risk for Meningioma among Iranian born Jews that can be attributed to possible hereditary and genetic factors involved in this disease.

Materials and Methods

All benign Meningioma cases diagnosed in Israel from January 2000 to the end of 2009 were extracted from the Israel national Cancer Registry (INCR) database. The INCR is a national population based tumor registry that was established in 1960 and is in operation since than. Reporting in Israel is mandatory since 1982 and all medical facilities (including hospitals owned by the government and privates, pathology laboratories) report to the registry by sending a copy of the original documentation to the registry. Cancer registration used by the INCR follows the internationally accepted rules (the IARC and the USA-SEER program). Site coding is done by the third version of the ICD-O coding system and the same system is used for morphology coding. Other medical data items are being coded according to the SEER system with some adjustments and are publicly available through the Middle East Cancer Consortium (MECC) web site. The INCR also gets detailed death files from the Central Bureau of Statistics and updates cases based on death certificates. Demographic data are being retrieved from the central population registry where data on all Israeli citizens are stored. In Israel each citizen (upon birth or immigration) has a unique identification number that is in use for all medical contacts. The population database contains also various demographic data including place (country) of birth and immigration date. These data items are electronically transferred to the INCR database for each cancer case.

The Israeli law established certain compensation to those who were irradiated and developed Meningiomas (as well as other tumors and diseases) and an administration to handle the thousands of claims was established, as well as research institute (Israeli law for compensation of tinea capitis victims, 1984; Modan, 1997; Sadetzki et al., 1999). In this specific case the INCR completeness is being monitored with the help of these structures. Benign brain tumors are also collected in Israel for more than 50 years and completeness of brain tumors registration at the INCR is 95% (Fishler et al., 2003).

Population data were retrieved from the Central Bureau of Statistics and were limited to the entire population (subdivided by 10 years age groups) living in Israel. We had no data on the gender breakdown but, looking at brain tumors in the Israeli population (Barchana and Liphshitz, 2007: www.health.gov.il/icr) shows that there is a small difference between male and female both for malignant tumors and all tumors (including benign). Therefore we believe that lumping both genders should not affect the overall result.

We included all intracranial (ICD-O version 3 code c70.x) meningiomas (ICD-o codes range 95000-95xxx) in Israeli citizens that were diagnosed in Israel in the period 01/01/2000 to 31/12/2009. All cases included in the analysis had a histopathology report stating the tumor was a meningioma. Patients that were born in Iran, Iraq, Turkey, Bulgaria and Greece were used for the analysis (Bulgaria and Greece were lumped together because the population data is set in this way and the small number of cases born in Greece). We calculated adjusted incidence rate for 100.000 people and computed Standardized Incidence Ratio (SIR) comparing the Iranian-born to each of the three other groups. A confidence interval of 95%

Table 1. Number of Cases by Period of Diagnosis and Age Groups in the Four Comparison Groups

Place of Birth		Iran		Turkey		Bulgaria and Greece		Iraq	
		Cases	Cumulative Percent	Cases	Cumulative Percent	Cases	Cumulative Percent	Cases	Cumulative Percent
Meningiomas, New cases, 2000-2009 by place of birth and age group at diagnosis									
Diagnosis year	2000-2004	73	59.8	32	51.6	19	54.2	96	49.4
	2005-2009	49	100	30	100	15	100	98	100
	Totals	122		62		34		194	
Age group:	15-44	4	3.3						
	45-54	16	16.4	4	6.45	2	6	17	8.8
	55-64	44	52.5	18	35.3	10	35.3	67	43.3
	65-74	35	81.8	22	71	8	58.5	54	71.1
	75+	23	100	18	100	14	100	56	100
	Totals	122		62		34		194	

Table 2. Standardized Incidence Ratio, Meningiomas in Iranian Israeli Jew

Comparison			Confidence Interval	
Observed cases	Expected cases	Standardized Incidence Ratio (SIR)	Low	High
Iran born *vs* Turkey born				
122	83.48	1.46	1.2	1.72
Iran born *vs* Bulgaria and Greece born				
122	65.7	1.86	1.53	2.19
Iran born *vs* Iraq born				
122	115.52	1.06	0.87	1.24

was used to test significance.

Results

A total of 412 benign meningiomas were included in the analysis. 29.6% of them (122 cases) in the Iranian-born group, 14.7% (62) were born in Turkey, 8% (34) in Bulgaria and Greece and 46% in Iraq. The average age at diagnosis was 68.6 for the entire group with ranges from 65.04 (SD 11.87) in the Iranian to 71.35 (SD 11.07) in the Bulgaria-Greece groups. Differences were not statistically different.

The Iranian-born population accounted in 2008 47,000 members those who were born in Turkey amounted to 25,800, 16,900 were of the Bulgaria-Greece group and 64.100 came to Israel from Iraq. In all groups the largest age group was 55-64, reflecting the immigration in Israel in the fifties of the previous century.

The comparison of incidence in Iranian-born versus those who were born in Turkey yield a Standardized Incidence Ratio (SIR) of 1.46 and was statistically significant. A higher SIR was noted when the group was compared to the Bulgaria-Greece group – 1.86, statistically significant and there was a small increase in risk for the Iranian born group were compared to those who were born in Iraq (1.06, not significant).

Examination of the Incidence Rate Ratio (RR) in the various age groups shows that in the 55-64 age groups rates are higher in Iranian-born when compared to Bulgaria-Greece and Iraq and RR is 1.28, 1.4 respectively. The last age group, the 75 and more shows almost a two times fold increase in incidence in the Iranian-Born compared to the Turks, a RR of 3.5 compared to the Bulgaria-Greece group and a 50% higher incidence than in the Iraqi group.

Discussion

The Israeli Jewish population is composed of immigrants from over 100 countries and their descendants. These days more than half of the population was born in Israel but as cancers are frequent in elderly, most of cancer cases being diagnosed in the country occur in the part of the population that was born outside Israel.

Results of our work confirm previous observation of a high incidence of brain meningiomas in the Iranian Jewish population (Preston-Martin et al., 1989; Inskip et al., 2003; Taghipour et al., 2010) and SIR's were at 1.6-1.8 levels. It is interesting to note that when compared to Iraqi born Jews incidence rate were similar to the study population. In order to test whether the observation can be limited to Jews born in Iran we choose to compare incidence rates to those in Jews originating in adjacent countries (Turkey and two Balkan states) where population mixture could more easily occur and therefore a finding of higher rates in Iranians has a stronger effect.

The strongest known risk factor for brain meningioma is exposure to ionizing radiations from medical procedures (and a much smaller amount from natural sources). The population under investigation was not massively affected with tinea capitis and did not receive scalp irradiations, and therefore this iatrogenic cause for increased risk of meningioma does not apply to this group. Other causes that were investigated (such as hormonal causes, injuries or exposure to chemicals) are potentially general risk factors that cannot be attributed to specific population (based on their origin). All those risk factors, including irradiations, are prevalent in the entire Israeli society, and demographics shows that there is no clear aggregation of Iranian-born people in certain areas in the countries (that may have hint increased exposure to environmental pollution or background radiations).

The state of Israel was established in 1948 and most people from those countries came in early fifties. It is interesting to note that RR of the elderly population (≥75 years of age) have higher incidence ratio than the in younger groups and that there is a positive correlation between age group and RR. This observation can hint to environmental factors that acted years ago in Iran play a role in Meningiomas occurrence and people who

immigrate to Israel when they were already adults were exposed to and therefore have higher rates of Meningioma than those who immigrates in young ages. Furthermore, in the eldest age group there was a substantial difference between Iranian and Iraqi born population, that can support this conclusion. It seems that those factors play only a part of the role since younger populations also have higher rates that in the neighboring populations.

There are several medical conditions and diseases that characterizes Jewish populations born outside Israel, to mention BRCA mutation found predominantly in European born Jewish women, Kaposi's Sarcoma in Jews originating in Hungary and CJD prevailing in Jews born in Libya (Poncz et al., 1982; Gabizon et al., 1994; Surrey et al., 1985; Ben-Dov et al., 1999). Traditionally the Jewish population is subdivided in Ashkenazi and Sepharaditic where the first group constitutes Jews originating from European countries and the Sepharaditic are those coming from North African and Asian countries, mostly Iran and Iraq. The distinction of these two group is in their religion customs including nutrition that were influenced by their hosting countries, as well an inter-community marriage there were frequent in those communities and therefore the possibility of founder mutations effects (Kaback et al., 2010; Dinour et al., 2011; Mukherjee et al., 2011). In order to avoid a potential bias in the comparison of neningiomas rate in the Iranian-born Jews, given the high rate of the disease in Sepharaditic Jews in Israel [due for the most to the scalp irradiation (Modan et al., 1977; Ron et al., 1988; 1991; Levin et al., 1995; Sadetzki et al., 2005)] we compared rates in this population to three other populations originating in the same geographical region: those originating in Iraq, in Turkey and in Bulgaria and Greece. Sepharaditic (where Sepharad means Spain) is a name given to Jews descended from the Jews of the Iberian Peninsula before their expulsion in the late 15th century. Following the Alhambra decree (1492) they settled in areas ruled by the Ottomans including North Africa, Turkey and Balkan states (Jewish History Sourcebook, 2012) Genetic studies demonstrated that most Jewish communities have remained relatively isolated from neighboring non-Jewish communities during and after the Diaspora; Along history there was a mixture of population in the last centuries when the Ottoman Empire ruled the region and genetically wise there could have been some mixture of Jews born in those adjacent countries "dissolving" the effect of a probable founder mutation in the region. Other factors, such as environmental or nutritional (Michaud et al., 2010) can explain the finding of a relatively lower SIR's in younger populations in relation to meningiomas.

There could not be a direct comparison to the findings by Taghipour and colleagues (Taghipour et al., 2010) since their report uses prevalence data while we use incidence from a registry.

A major limitation of this study is it's ecological nature, where individual risk factors of neither group are known. There are two basic common denominators to the populations presented that may be related to development of menungiomas: their genetic origin and life style. Other factors that can be determinating in meningimas (such as environmental factors) could not be assesses, but we do not believe that those differences are of a major impact to bias the results.

In conclusion, higher rates of Meningiomas were seen in Jews originating in Iran that are living in Israel as compared to rates in neighboring countries of origin. These differences can bein part attributed to early life environmental exposures in Iran but probably in larger amount are due to genetic and hereditary factors in a closed community like the Iranian Jews. Some support to this conclusion was also found in other published research.

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