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RESEARCH

Risk of Subsequent Primary Tumor Development in Melanoma Patients

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Abstract Incidence of subsequent malignant tumor development in 740 patients with primary cutaneous melanoma verified between 2006 and 2010 at the Semmelweis University was studied retrospectively and was compared to data of sex and age matched Hungarian population. The follow-up period was 1499 person-years for the whole group from the diagnosis of index melanoma with an average of 2 years. Standardized incidence rate (SIR) was established as the ratio of observed and expected values. The risk of all subsequent malignancies was 15- and 10-fold higher in males (SIR: 15.42) and in females (SIR: 10.55) with melanoma, than in the general population. The increased cancer risk resulted mainly from the significantly higher skin tumor development: SIR values were 160.39 and 92.64 for additional invasive melanoma and 342.28 and 77.04 for subsequent in situ melanoma in males and females, respectively. Non-melanoma skin cancers also notably contributed to the higher risk, the SIR was elevated in both genders to the same extent (males: 17.12, females: 17.55). The risk was also significantly higher for extracutaneous tumor development like chronic lymphocytic leukemia, colon and kidney cancer (both genders), non-Hodgkin's lymphoma, cervical cancer (females), and bladder carcinoma (males). These data underline the importance of patient education and the necessity of frequent medical follow up, including a close-up dermatological screening of melanoma survivors for further malignancies.

Keywords Melanoma · Survivor · Cancer risk · Subsequent primary tumor

Abbreviations

ALL	Acute lymphocytic leukemia
CLL	Chronic lymphocytic leukemia
CI	Confidence interval
E	Expected value
EAR	Excess absolute risk
MM	Malignant melanoma
NHL	Non-Hodgkin's lymphoma
NMSC	Non-melanoma skin cancer
NOS	Not otherwise specified
O	Observed value
SEER	Surveillance Epidemiology and End Results
SIR	Standardized incidence rate
PYR	Person year
UV	Ultraviolet

Introduction

Over the past decades a number of studies investigated the risk of subsequent primary malignancy development in malignant melanoma (MM) patients (Table 1). Although few studies reported both increased and decreased risk for de novo second malignancies [2, 9–11], the majority of investigators observed increased de novo tumor development, particularly MM [1–3, 6, 10, 12–17] and non-melanoma

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skin cancers (NMSC) among MM Survivors [1–4, 7, 11, 17, 18] compared to the general population. Out of the further primary malignancies non-Hodgkin's lymphoma (NHL) [3, 5, 7–10, 13–15], breast [3, 10, 13, 14], kidney [6, 9–11, 13, 14], prostate [2, 10, 13, 14], soft tissue [10, 13, 14], brain and nervous system cancers [1, 13], bone cancer [11, 13], chronic lymphocytic leukemia (CLL) [13–15] occurred in excess among MM survivors. The largest study included 89 515 patients and reported a 9-fold risk of subsequent MM development, also an increased risk for female breast cancer, prostate cancer and NHL [14].

In our department the number of new MM cases varies between 120 and 170 yearly. The aim of the present work was to evaluate the risk of subsequent primary tumors among our patients and to compare these results with data of the Hungarian National Cancer Registry and also with international databases. We separately evaluated the risk of tumor development in patients with multiple primary MM.

Methods

Clinical data of 740 patients with primary invasive MM between January 1, 2006 and December 31, 2010 have been retrospectively analyzed. All patients underwent surgical excision and the diagnosis of MM was histologically verified in the same dermatohistopathological laboratory. The gender, the age of patients, the histological type and the Breslow thickness of the MMs were collected for the present study. The second tumors were mostly detected by the regular dermatological controls and medical imaging techniques during the follow-up period and were verified by histology. Additionally, we identified the patients with multiple primary MMs. To uncover possible detection bias due to the enhanced medical screening during the MM staging period we performed sensitivity analysis; we excluded the 8 subsequent malignancies reported in the first 2 months after the diagnosis of the primary MM.

Table 1 Second primary tumor risk among malignant melanoma (MM) survivors

Number of MM patients	Follow- up period	Studied database	Increased (IR), lower (LR) or not increased (NI) tumor risk [Reference No.]
20 354	1958–1988	Swedish Cancer Registry	IR: all second primary cancers, MM, NMSC, nervous system, colon cancer (men) [1]
1 780	1974–1994	Cancer Registries of two Swiss Cantons	IR: MM, basal and squamous cell, prostate carcinoma. NI: non-skin tumors [2]
3 766 in situ MM	1958–1992	Swedish Cancer Registry	IR: all second primary cancers, MM, NMSC, breast cancer, NHL (females), multiple myeloma, colon, pancreas carcinoma [3]
1 396	1977–1978	Detroit area	IR: basal, squamous cell carcinoma [4]
54 803	1973–1996	SEER program	IR: NHL [5]
4 597	1977–1992	Ludwig-Maximilians-University	IR: MM, kidney carcinoma (men) [6]
1 835	1985–1999	Tuscany Cancer Registry	IR: all second primary cancers (<60 years), NMSC, NHL [7]
109 532		Data from seven cohort studies	IR: NHL [8]
955	1978–2001	Indiana University Cancer Center	IR: NHL, renal cell carcinoma (men) NI: non-skin tumors (females) [9]
66 059	1972–2000	SEER program	IR: MM, breast, prostate cancer, NHL, soft tissue, kidney cancer LR: lung, bronchus, larynx, gum and mouth, esophagus, pancreas, stomach, cervical cancer [10]
14 560	1985–2002	Italian Network of Cancer Registries	IR: NMSC, bone, kidney cancer LR: liver, lung cancer [11]
1 839	1993–2002	Northern Ireland Cancer Registry	IR: all second primary cancers, MM (men) [12]
16 591	1973–2003	SEER program	IR: MM, soft tissue, bone and joint, thyroid, kidney, nervous system, prostate, breast cancer, CLL, NHL [13]
89 515	1973–2006	SEER program	IR: MM, breast, prostate, small intestine, kidney, thyroid, soft tissue, salivary gland cancer, NHL, CLL [14]
(1) 76 041 invasive MM (2) 40 881 in situ MM	1992–2006	SEER program	1. IR: MM, thyroid cancer, CLL, NHL 2. IR: invasive MM, CLL [15]

Statistics

Indirect Standardization: Data obtained from our department (sample) were compared with that of the Hungarian Cancer Registry [19] (population). We estimated the difference between observed (O) and expected (E) values dividing them into two age groups (below 50 and over 50 years) according to the age at the time of the primary MM diagnosis. Standardized incidence rate (SIR) was then established as the ratio of O and E values (SIR = O/E). The confidence intervals were approximated after Rothman and Boice [20]. We accepted a significant difference between O and E values at the 0.05 % level, if the 95 % confidence limits excluded unity. Excess absolute risk (EAR: expressing the difference of the absolute risk between sample and control population) was calculated on the basis of person years (PYR) data obtained in the sample and in the population (EAR = 10^5(O-E)/PYR). PYRs were accumulated from the time point of the diagnosis of the first melanoma until the last control examination, death, or December 31, 2010. We also tested, if there was significant difference between genders and/or age groups. This estimate was based on a Pearson-Yates test [21, 22]. Values were expressed as mean ± standard deviation.

Results

The Characteristics of the Patients and the Primary Melanomas

During 5 study-years 740 new MMs were diagnosed at our department. The rate of males (n=366, 49.5 %) and females (n=374, 50.5 %) was about the same. The median age at the diagnosis was 59.39±16.66 years (mean ± standard deviation), males: 60.07±16.50 years, females: 58.73±16.81 years. Most MMs were diagnosed in 2008 (n=171). Except 2008 and 2010 more cases were verified among females than males. The Breslow thickness showed highly different values (between 0.2 and 52 mm), in average 4.7 mm±13.7. The median Breslow thickness was almost 1 mm higher in males (5.1 mm±14.2) than in females (4.2 mm±13.3). The most frequent histological type was superficial spreading melanoma (SSM) in both genders (more than 60 % of all tumors) moreover, 71 % of the second malignancies developed in those patients who had this histological type.

Further Primary Tumor Development

The whole follow-up period included 1 499 PYRs (males: 672.4, females: 776.6), in average 2±1.5 years. 115 second tumors were diagnosed (males: 64, females: 51). 70 (9.5 %) patients had one, 16 (2 %) patients had two, while 1 (0.1 %) patient had three subsequent cancers. The distribution of second malignancies was the following: 50 % NMSC, 30.4 % MM (15.6 % in situ MM, 14.8 % invasive MM), 4–4 % lung and colon carcinoma, 3–3 % CLL and kidney carcinoma. Each of NHL, female breast, cervical, prostate, bladder and not specified tumor occurred in 1 %, respectively.

Multiple MMs were diagnosed in 44 patients (6 % of all patients): out of them 32 patients developed two, 10 patients three, and 1–1 patient four and five primary MMs. The incidence of multiple MM was higher among males (61 %, n=27), than in females (39 %, n=17). Out of the 44 multiple MM patients 34 developed subsequent MM in the observation period (17 invasive and 17 subsequent in situ MMs). In 7/44 (16 %) multiple MM patients additional non-melanoma malignancy was observed: we noticed 5 NMSCs (71 % of the second tumors), 1–1 kidney and colon cancer. In contrast the rate of NMSCs among the second primary tumors of all MM patients was 50 % (n=58).

The Risk of Subsequent Primary Tumor Development in MM Patients

The risk according to gender and age (below 50 and over 50 years) was evaluated. Among the primary MM survivors the overall risk of a subsequent primary tumors was increased 15-fold in males, 10-fold in females compared to the general population (males: SIR: 15.42, O: 61, 95 % CI: 15.34–15.51, EAR: 0.32; females: SIR: 10.55, O: 51, 95 % CI: 10.49–10.60, EAR: 2.81) (Table 2).

The elevated tumor risk was primarily due to additional cutaneous malignancy development, including primary MM. The risk of in situ MM was highly elevated in both genders, but in males (SIR: 343.28) the risk was more than 4 times (p<0.05) higher than in females (SIR: 77.04). Subsequent invasive MM cases also contributed notably to the elevated overall tumor risk. We experienced significantly elevated risk both in males and in females; high SIR values (males: 160.39, females: 92.64) were observed in patients <50 years, in addition the SIR was significantly higher among males than females. NMSCs occurred also with elevated risk, the SIRs showed significantly higher risk in both age groups compared to general population (males: 17.12, females: 17.55) without significant difference between the genders. We studied the risk of Bowen's disease separately from other NMSCs. We had cases only in age group under 50, and found the SIR more than double in males (SIR: 25.63) than in females (11.55).

Additionally, some non-cutaneous primary cancers also presented with significantly increased risk: CLL had an elevated SIR in both genders, but was higher among females (males: 8.41, females: 23.56). Colon-sigma and kidney cancers occurred with significantly higher risk in both genders, cervical

cancer and NHL only in females, while bladder tumor was in excess in males.

On the other hand, the risk of lung and prostate cancer in males, breast cancer in females was found significantly lower compared to general population.

We performed sensitivity analysis by the exclusion of 8 subsequent primary tumors detected within 2 months following the first MMs verification. When we excluded these cancers, the risk of female's Bowen's disease was no longer significantly higher and the difference of CLL risk in males and females was not any more significant (Table 2. data in italics).

Discussion

The aim of this study was to investigate, whether the risk for second primary cancer development is higher among MM patients than in the general population in Hungary. We also wanted to study the incidence and type of different secondary malignant tumors. While the results of this paper are consistent with most previous studies, there are some differences between our findings and the international data. As in most studies, we also found elevated overall risk for subsequent primary tumors [1, 3, 7, 12–14, 18]. In our patients this risk was generally 15-fold higher in males, 10-fold higher in females compared to the age and gender matched population (males: SIR: 15.42, EAR: 0.32; females: SIR: 10.55, EAR: 2.81) in Hungary.

From the 115 subsequent cancers 93 (81 %) were skin tumors (NMSC: 58, MM: 35): that means, that the increased overall tumor risk was majorly due to new cutaneous carcinoma and MM development. Our results are in agreement with most international data [1–4, 6, 7, 10–18]. The dramatically increased risk of subsequent MM can be the result of germ line or somatic mutations in e.g. CDKN2A, CDK4,

Table 2 Risk of the subsequent primary malignancies after primary melanoma among our patients

Subsequent tumor	Age group	Male				Female				M/F
		O	SIR	95 % CI	EAR	O	SIR	95 % CI	EAR	
In situ melanoma	50<	15	343.28*	(317.92–370.12)	220.59	3	77.04*	(71.58–82.8)	40.12	+
		14	*320.39**	(*296.71–345.46*)	*206.15*	–	–	–	–	+
Invasive melanoma	<50	1	160.39*	(147.89–173.66)	0.14	2	92.64*	(88.16–97.28)	12.33	+
	50<	8	14.43*#	(14.13–14.75)	0.43	6	32.98*#	(31.88–34.1)	16.91	+
		–	–	–	–	*5*	*27.48*#*	(*26.57–28.42*)	*14.01*	+
NMSC	<50	–	–	–	–	1	23.02*	(22.23–23.82)	2.96	+
	50<	27	17.12*	(16.90–17.34)	10.61	27	17.55*#	(17.34–17.75)	8.76	–
		24	*15.60*#*	(*15.42–15.78*)	*7.73*	–	–	–	–	–
Bowen's disease	50<	2	25.63*	(24.19–27.13)	16.21	1	11.55*	(11.00–12.12)	0.34	+
		–	–	–	–	*0*	–	–	–	–
Cervical cancer	<50	–	–	–	–	1	34.74*	(33.29–36.25)	4.54	–
CLL	50<	1	8.41*	(8.03–8.81)	4.88	2	23.56*	(22.42–24.74)	11.94	+
		–	–	–	–	*1*	*11.78**	(*11.21–12.37*)	*5.71*	–
NOS tumor	50<	–	–	–	–	1	8.57*	(8.22–8.94)	4.01	–
NHL	50<	–	–	–	–	1	7.61*	(7.32–7.92)	3.5	–
Kidney cancer	50<	2	5.39*	(5.25–5.53)	2.89	1	4.42*	(4.29–4.55)	1.81	–
		1	*2.7**	(*2.63–2.77*)	*1.12*	–	–	–	–	–
Colon, sigma cancer	50<	4	3.83*	(3.77–3.89)	1.87	1	1.28*	(1.25–1.3)	0.15	+
Bladder cancer	50<	1	2.7*	(2.63–2.77)	1.12	–	–	–	–	–
NOS female cancer	<50	–	–	–	–	1	1124.98*	(871.80–1428.7)	149.12	–
Lung cancer	50<	2	0.92*	(0.91–0.93)	−0.05	2	2.06*	(2.03–2.09)	0.56	–
Prostate cancer	50<	1	0.76*	(0.75–0.77)	−0.18	–	–	–	–	–
Breast cancer	50<	–	–	–	–	1	0.09*	(0.09–0.09)	−3.49	–
Total		64	15,42*	(15.34–15.51)	0.32	51	10.55	(10.49–10.6)	2.81	+

*, +, and # denote significant difference between observed and expected values, sexes, and age groups (designated at the higher age group)

CI confidence interval, *CLL* chronic lymphocytic leukemia, *EAR* excess absolute risk, *M/F* male/female difference, *NHL* non-Hodgkin's lymphoma, *NOS* not otherwise specified, *NMSC* non-melanoma skin cancer, *O*: observed value (here: number of second primary tumors), *SIR* standardized incidence rate

MC1R, MITF, BRAF, KIT [23, 24], but could be also induced by severe and/or long lasting UV radiation or other environmental factors, including also cancer and MM treatment. Recent observation disclosed that the BRAF inhibitor therapy for metastatic MM commonly triggers secondary skin cancer development through CRAF activation and HRAS mutation induction [25, 26]. This therapy was also complicated by secondary RAS mutant leukemias, colonic adenomas, gastric polyps [27, 28]. Also, in case of RAS mutant cancer in the medical history BRAF inhibitor treatment should be applied particularly carefully [29]. None of the patients included in the present study had been treated with BRAF inhibitor.

Beside the almost equal number of studied males and females (366 and 374, respectively), we experienced more than 100 PYR shorter follow-up period and almost 1 mm higher median Breslow thickness among males. The increased subsequent MM risk, the shorter follow-up period and the later tumor verification may reflect the worse compliance of males in terms of UV protection and medical examinations.

Beside the additional skin tumors, we found significant excess risk in case of some internal malignancies. As Bhatia et al. [16], we also found higher risk for bladder tumor in males. The higher risk for CLL among our patients agrees with the results of some SEER program based studies [13–15]. NHL occurred with higher risk only in our female patients, while more authors found a generally elevated NHL risk among MM survivors [3, 5, 7–10, 13–15]. Recently Lens et al. [8] conducted a study on MM and NHL, and confirmed a bidirectional association between the two primary malignancies. The possibility of common risk factors, e.g. immunological ones (increased risk of both malignancies in immunosuppressed patients [14]) and environmental ones (UV) have been discussed [30–32].

We experienced lower risk for subsequent lung cancer in males in accordance with the findings of Freedman et al. and Crocetti et al. [10, 11], who explained the lower pulmonary cancer risk mostly with the lower smoking rate in the higher socioeconomic group of MM survivors [10]. We found significantly lower risk of prostate tumor among our male patients and breast cancer in our female patients, which are contradictory with some other studies, where breast [3, 10, 13, 14] and prostate [2, 10, 13, 14] cancer occurred with higher risk. On the basis of UVB - vitamin D cancer hypothesis the personal solar UVB irradiation may reduce beside several other tumors the risk for breast, endometrial, prostate, renal and colon cancer [32–35]. While the high personal UV exposure is a risk factor of melanoma, the protective role of sunlight can explain the lower incidence of prostate and breast cancer among our MM patients. In this study the risk of kidney and colon cancer was higher, similarly to some previous publications [1, 3, 6, 9–11, 13, 14]. Some studies reported the UV irradiation as a protective factor against these extracutaneous malignancies [32–35].

To our knowledge only Manganoni et al. [18] analyzed the incidence of subsequent primary cancers in patients with multiple MM. In their study the percent of multiple MM among all MM cases was 3.5 %, while we found a higher, 5.9 % proportion. Interestingly the ratio of second primary cancers (16 %) was identical with ours, while the ratio of NMSC was 59 % in their study, while among our patients this value was again higher (71 %).

Statistics: The limitation of this study might be the relatively small number of MM cases. The use of sensitivity analysis might change the results of subsequent tumor analysis in MM patients [15], like among our patients the risk of Bowen's disease among MM females was not any more significantly elevated, and the difference in the likelihood of CLL development between genders was no longer significant.

The data of this study confirm a more than 10-fold increased risk for additional malignancies in both male and female MM patients. This excess is primarily due to the significantly increased risk for subsequent skin tumors: in situ and invasive MM and NMSC had equally high SIR. Among the studied 740 MM patients 81 % of all subsequent malignant tumors developed on the skin, while in the general population skin tumors formed only 34 % of all tumors [19]. The especially elevated SIR for secondary in situ MM may reflect the effectiveness of the advanced dermatological screening after the primary MM, but also the persistence of pre-existing tumorigenic genetic or environmental factors for MM. The risk of CLL in both genders, and that of NHL in females also proved to be significantly elevated compared to the control population. These data underline the necessity of careful follow up of MM patients, not only for invasive MM propagation, but also dermatological and hematological screening. Furthermore, any internal tumor or metastasis should be histologically verified, even in late stage of progressive MM.

In conclusion primary MM survivors have highly elevated risk to develop subsequent malignancies, particularly skin tumors. Our study emphasizes the importance of the regular medical, particularly dermatological controls to identify possible second skin or internal malignancies at early stage.

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