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Melanoma incidence increase in the elderly of Catalonia with stabilization of incidence in the younger population: effect of prevention or consequence of immigration?

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Abstract

All cases of MM diagnosed in 23 Hospitals in Catalonia, from 2000 to 2007 were recorded and its incidence calculated and adjusted for the European standard population through the direct method. The age standardized rate varied from 6.74 in 2000 to 8.64 in 2007 for all melanomas and from 4.79 to 5.80 for invasive MMs, the Breslow thickness being stable during the period. The increase in invasive melanoma incidence in the elderly was remarkable, the crude rate increasing from 11.04 (2000) to 15.49 (2007) in the 60–64 yr population, while remaining more stable from 3.97 in 2000 to 4.55 in 2007 for the age range of 30–34 ys or with a tendency to decrease from 5.1 in 2000 to 2.5 in 2007 for age range of 25–29 yr, age ranges much more affected by immigration. Despite the large immigrant population (nearly one million immigrants that arrived in Catalonia during the study period from countries with a low melanoma incidence), melanoma incidence in our region has risen considerably and this trend will likely persist in the near future.

Keywords

melanoma; hospital based registry; incidence; epidemiology; skin cancer

Introduction

The incidence of cutaneous malignant melanoma (CMM) has increased in recent decades more than any other malignant neoplasm (1)(2). In the United States, the number of melanomas diagnosed increased 619% and the mortality increased 165% between 1950 and 2000 (2). The highest incidence rates of CMM have been observed in Australia and New Zealand followed by North America and Northern Europe (1)(3)(4)(5). The incidence and mortality of melanoma in people living in Europe varies considerably between countries (6). The highest incidence rates are found in northern and western countries and the lowest in southern countries (1). These variations are likely to be linked to specific behaviour (winter holidays, sun-seeking behaviour) as well as prevalent skin phototype and other clinical

characteristics of the population such as the number of nevi or the prevalence of red-hair (7). Some regions have reported a declining trend in melanoma incidence, while in others the rise in incidence persists (8)(9).

Spain has one of Europe's lowest incidence and mortality rates. Although there are only a few studies on the epidemiology of melanoma in Spain, an increase in incidence over the past decades has also been reported here (10).

Catalonia is a region, located in the North-eastern part of Spain composed of the provinces of Lleida, Girona, Tarragona and Barcelona. In our region, Catalonia, only two cancer population registries exist which together covered a population of 1,174,977 in 2001, representing only 19% of the total Catalan population living in an area far away from the city of Barcelona and most populated cities of the region. According to these registries, over the past 20 years, CMM incidence has increased substantially at a faster rate than any other neoplasm in Catalonia (11). Marcos-Gragera et al, suggested that this trend will probably continue for the next few years. Nevertheless, CMM mortality trends have already been published the crude rate in the period 2000–2004 being 2.52 for men and 2.11 for women and in the period 2005–2009 2.72 for men and 2.28 for women (cure rates per 100 000 person-years) (11). On the contrary, epidemiological data from other regions of Spain suggested that melanoma mortality rates has been decreasing over the past 10 years, at least in males (12).

A study performed in one hospital from our region reported an increase in the incidence of both *in situ* and invasive melanomas and among the invasive melanomas not only thin melanomas increased but also thick ones with a resulting stable mean Breslow thickness of 1.9mm (13).

Knowledge of the global incidence of melanoma in our region is crucial for public health care organization, but also knowing the distribution according to Breslow thickness, age, gender, subtype of melanoma or localization would help to establish adequate preventive or early detection policies to targeted population.

Rationale

To perform a Hospital-based registry of melanoma covering all Catalonia in order to describe the incidence of *in situ* and invasive melanomas diagnosed in the region over an 8-year period from 2000 to 2007 and their clinico-pathological characteristics.

Methods

Twenty-three Hospitals covering most of the population of Catalonia, 7M inhabitants, reported the melanoma cases diagnosed from 2000 to 2007. Five of the Hospitals are tertiary-care Hospitals located in Barcelona and its suburbs. The remaining Hospitals are Community-based Hospitals and one private Hospital.

Data collected included date of birth, gender, date of diagnosis, location of the melanoma, histopathological subtype, Clark Index, Breslow thickness and presence of ulceration. Data

was recruited from the melanoma-unit's databases when available (Hospital Clinic de Barcelona, Hospital de Bellvitge and Hospital Germans Trias I Pujol). For the remaining hospitals, data was retrospectively collected for the first five year period (2000–2005), and prospectively for the period 2006–2007.

Statistical Analysis

Incidence rates were age-standardized through the direct method using the European standard population. Categorical variables compared by means of the chi-square test, or the Fisher's exact test, when the expected observations were less than five. For continuous variables mean and Standard Deviation (SD) were reported. The student t student test was used to compare the means between males and females. To detect differences in means of age and Breslow thickness across the years Two-way ANOVA tests were conducted. Statistical analyses were performed with SPSS 10.0 and STATA10.

Results

A total of 5407 cases were reported in the 8-year study period (2000–2007); 408 cases were reported by more than one centre and thus duplicated. In all these cases one of the entries was eliminated. Ultimately, 4999 melanoma tumours were included in the study. One third (33%) of cases were reported by one referral centre in Barcelona (Hospital Clinic Barcelona) and 26% were reported by the other two referral hospitals in Barcelona's suburbs (Hospital de Bellvitge and Hospital Germans Trias I Pujol) together. In 3884 cases the melanoma was invasive and the remaining 1125 were *in situ*. Females had 2748 cases of melanoma (55%), whereas men had 2216 cases (44.3%). In 35 cases, gender data was not available. An increasing trend in the number of incident cases of melanoma was observed throughout the study period (494 cases in 2000; 619 in 2001; 590 in 2002; 556 in 2003; 583 in 2004; 714 in 2005; 691 in 2006 and 739 in 2007) (Table I). The total crude rate for melanoma (including *in situ*) per 100,000 inhabitants increased from 7.74 in 2000 to 10.13 in 2007 and the age standardized rate for the European population increased from 6.74 in 2000 to 8.64 in 2007 (Table I). For invasive melanomas the total crude rate per 100,000 inhabitants increased from 5.42 in 2000 to 6.77 in 2007 and the age standardized invasive melanoma rate for the European population increased from 4.79 in 2000 to 5.8 in 2007 (Table II). Crude rates and age adjusted for European population rates increased in both sexes (Table III). Detail of rates according to age and years (2000 to 2007) are detailed in supplementary Table I and figure 2.

The majority of melanomas were located on the trunk (37.5%) followed by lower extremities (20.1%), upper extremities (11.7%), face (11.4%), palms and soles (7.8%), head and neck (5.1%) and mucosa (1%). The location was not properly reported in 5.4% of tumours.

Histopathological characteristics

The most frequent histopathological subtype was superficial spreading melanoma (SSM) which represented 59.5% of the tumours, followed by Nodular melanoma (NM) (11.7%), Lentigo Maligna Melanoma (LMM) (8.4%) and Acral Lentiginous Melanoma (ALM)

(4.4%). In 11.4% of melanomas the histopathological subtype was not reported and in 2.6% it was unclassifiable. Infrequent subtypes of melanoma were Lentiginous melanoma of the mucosa (0.5%), desmoplastic (0.3%) and Spitzoid melanoma (0.2%).

The Clark level was not reported in 11.3% of the cases. In situ melanomas represented 25.5% of the tumours (Table IVa), Clark II 15.6%, Clark III 30.0%, Clark IV 17.3% and Clark V 3.6%. During the eight years of the registry, the incidence of in situ melanomas remained stable ($p=0.12$) (table IVa).

The distribution of melanomas according to Breslow thickness also remained stable during the study (Table IVb). Mean Breslow thickness remained stable throughout the study period (table V) while mean age at diagnosis increased during the period (Table V). Only 13% of cases were reported as ulcerated, but the presence/absence of ulceration was not reported in 24% of cases.

The mean age at diagnosis varied according to the histopathological subtype being younger in SSM (mean 52.6 yrs) and Spitzoid melanomas (mean 50.6 yrs) compared to NM (mean 59.3 yrs), ALM (mean 63.01 yrs), mucosal (62.4 mean yrs) and finally LMM (70.3 mean yrs).

Trends by sex

As previously described in other populations, location of the melanoma differed significantly between Catalan women and men ($p<0.000$) (table VI). The trunk was the most frequent location in males (48.9%) followed by the face (11.4%). In females the trunk represented 28.5% of cases followed by, almost in equal proportion, the lower extremities 28.3%, then upper extremities (13.4%) and face (10.9%).

The mean Breslow also differed, being thicker in men (mean 2.3, SD 3.21) than women (mean 1.8, SD 3.1) ($p<0.001$).

Men were diagnosed at an older age (mean 57.7 yrs, SD 16.9) than women (mean 54.3 yrs, SD 17.9) ($p<0.01$) (see figure 1).

An increase in incidence was observed in both sexes.

Trends by subtype and age

The most frequent subtype of melanoma observed throughout the study period was superficial SSM in patients aged between 50–55 yrs. However, an increase in LMM was also detected among the elderly, commonly in their 70's.

Discussion

The incidence of melanoma has been increasing worldwide (1) but with differences according to the characteristics of the population living in a given country (skin type, red hair, etc), sunlight incidence during the year and sun-exposure behavior (14) (9) or even the effect of the Mediterranean diet (15).

Ribes et al, (16) performed a melanoma incidence projection in Catalonia for the period 2005–2019. Bayesian age-period-cohort models were fitted to age-specific rates for 1985–2004 to obtain the expected number of cases for the 5-year periods 2005–2009, 2010–2014 and 2015–2019. They estimated 307 new melanoma cases per year in men and 478 in women in the period 2005–2009 with a crude rate for 100,000 inhabitants of 10.43 in men and 15.57 in women and a world age standardized rate of 8.31 in men and 13.21 in women.

Our results confirm that melanoma has been rising considerably among men and women in Catalonia over the past decade and that this trend is likely to persist in the near future, as suggested by Ribes et al. (16) The incident cases that we reported are similar to those estimated by Ribes et al. while the crude rate and the age standardized rate were lower than expected according to their study. The immigrant population that has come to live in Catalonia has grown significantly in the past decade (supplementary table 1). From representing only 2.9% of the total population in Catalonia in 2000, this group grew to 13.1% in 2006 and reached 16.4% in 2010. They mainly originate from countries with pigmented skin population and/or low melanoma incidence (supplementary table 2). Among the different nationalities, the most frequent are: Moroccans (19.6%), Rumanians (8%), Ecuadorians (6%) and Bolivians (4.7%) (<http://www10.gencat.cat/gencat/AppJava/es/actualitat2/2010/dadesimmigraciacatalunya.jsp>).

One may hypothesize that the increasing number of new melanoma cases that we have observed has been diluted by the million immigrants that arrived in Catalonia during this period. In favour of this hypothesis is the fact that crude rates for invasive melanoma incidence increase from 11.04 in 2000 to 15.49 in 2007 for the population of 60–64 yrs, an age range less affected by immigration, while the crude rate remains more stable from 3.97 in 2000 to 4.55 in 2007 for the age range of 30–34 years old or with a tendency to decrease from 5.1 in 2000 to 2.5 in 2007 for age range of 25–29 years old (supplementary table 1 and figure 2), much more affected by immigration (usually being young people that migrate for work reasons as reflected in supplementary table 1). Another interesting observation from our study is the already known fact that Catalan women develop melanoma at an earlier age and are affected at different sites of the body compared to men. Melanoma appears mostly on the trunk in men, but in women it affects trunk and lower limbs in almost equal proportion. The reason why legs are commonly affected in women, but not in men, is unknown but similar in different populations. Other epidemiological studies of melanoma performed in central and northern Italy, where the climate and skin phototypes are similar to Catalonia, reveals that women are much more prone to develop melanoma on legs compared to men. The possible effect of intermittent sun exposure according to different dress in women (i.e. use of skirts or shorts) has been suggested as responsible for this increase in melanoma incidence on women's legs but probably this is not the main reason and other causes may be argued such as the genetic background of different subtypes of melanoma influenced by gender.

It is noteworthy that although the number of cases of melanoma was higher in women than men in Catalonia, the incidence increased in similar proportion in both sexes, suggesting that the increase in sun-exposure is similar between men and women but maybe the proportion of recreational and occupational exposure has changed between them.

The most frequent subtype of melanoma observed throughout the study period was SSM in patients aged between 50–55 years-old. However, an increase in LMM was also detected among the elderly, commonly in their 70's. This suggests that the incidence of melanoma increased not only among the young to middle aged population but also during the last decades of life. This increase in LMM may also be related to the fact that life expectancy has increased substantially over the past decades.

A reason why melanoma is diagnosed at an earlier age in women than men may be that women seek medical attention for skin conditions sooner than men but also may be related to the location of the tumour, more visible on lower limbs than on the trunk or especially on the back. This may also explain why the Breslow index was lower in women than men, as melanomas were detected at earlier stages. Depth of invasion, measured by the Breslow index, is the most important prognostic factor in melanoma survival. From our findings, it would be interesting to compare mortality rates due to melanoma in Catalan women and men. Unfortunately, mean Breslow thickness does not decrease during the follow-up period. This fact may be related to the increase in Clark IV and the steadiness observed in Clark V melanomas, or it may be related to nodular, rapidly-growing and invasive melanomas, which clearly have a distinct biological behavior compared with the slow-growing SSM rather than the prevention and early diagnosis campaigns. We have not observed an increase in the incidence of *in situ* melanoma regardless that physicians are now more aware and prepared to detect melanoma at earlier stages suggesting that population based strategies for secondary prevention should be improved or implemented in our region.

Our mean age standardized incidence rate of 5.27 for invasive melanoma is lower than the finding by Crocetti et al. (17) who reported that the standardized incidence rate for invasive melanoma rose from 6.4 in 1985–1989 to 13.6 in 2000–2004 in central Italy. Pellacani et al, (18) in northern Italy showed a standardized incidence rate of 9.7 for invasive melanomas and 11.9 when also considering *in situ* ones. However, when including *in situ* melanomas, our standardized incidence rate rose to 7.8. As nearly 20% of Catalan people have private insurance (http://www.csbcn.org/area_prov/doblecob_CSB.pdf) and this study was neither focused on private dermatologists nor private pathologists, any thin melanomas diagnosed in private practice and not sent to the referral hospital for treatment may have been lost. Taken together, these findings suggest that melanoma is rising in Catalonia, as in other Mediterranean countries, with a trend of increased mean age at diagnosis, an increase in *in situ* melanoma, but stable mean Breslow thickness with a possible dilution effect of new melanoma cases by immigration from low incidence melanoma countries suggesting that we should also register the origin of the patient as well as racial and cultural characteristics.

One limitation and possible bias of our study is that information was partially gathered retrospectively before 2005 and prospectively thereafter. However, it is the largest epidemiological melanoma study performed in Catalonia to date.

Melanoma incidence has risen significantly in the Mediterranean countries over the past decade and should be considered a public health care problem. Our findings may help to establish primary and secondary preventive measures aimed at a targeted risk-population. Further efforts are required to increase melanoma awareness in the general population and

the importance of early detection among the medical community if we want this increasing trend in incidence to stop.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation and acronym list

ALM	Acral Lentiginous Melanoma
CMM	cutaneous malignant melanoma
LMM	Lentigo Maligna Melanoma
NM	Nodular melanoma
SD	Standard Deviation
SSM	superficial spreading melanoma

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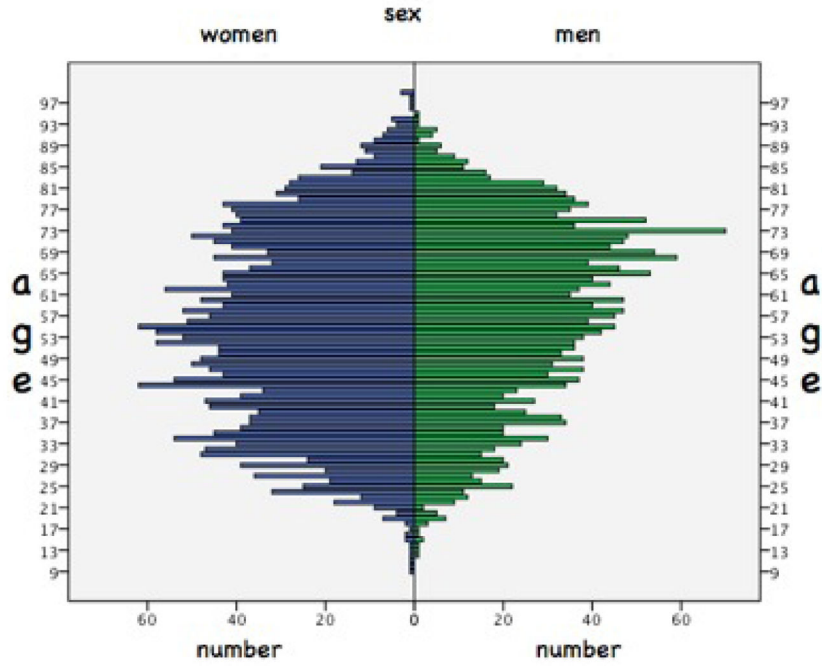


Figure 1.
Distribution of melanoma age of onset according to sex

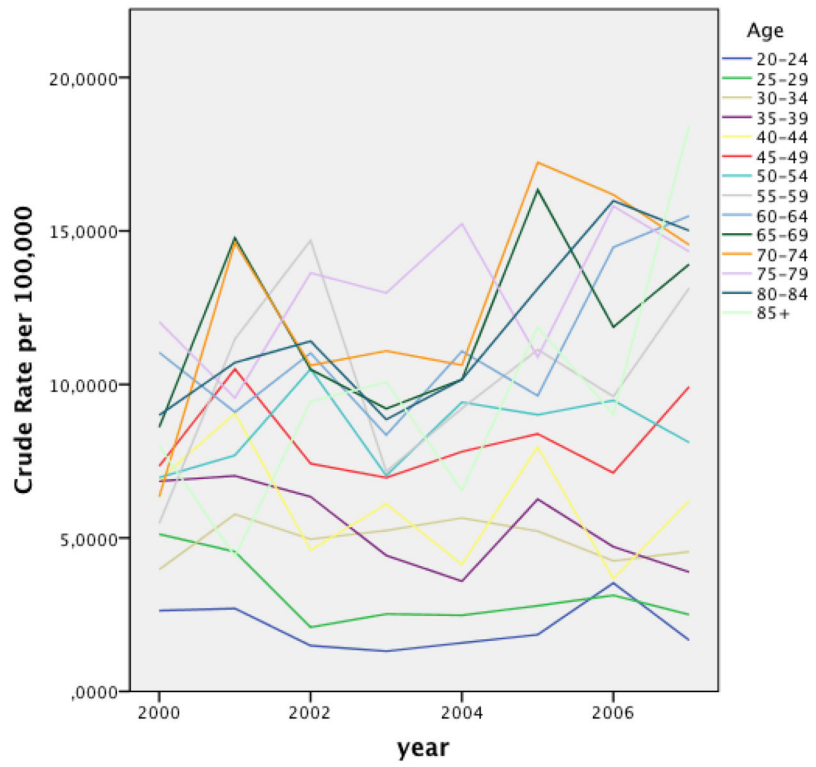


Figure 2. Variation of crude rate incidence taxes of invasive melanoma according to age during the period of the study.

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Table I

Incidence of melanoma (including *in situ* melanoma)

Year	Cases	Population in Catalonia	Crude Rate*	Age standardized rate**†	Truncate rate* (35-64)	Cumulative rate (0-74)
2000	481	6,213,904	7.74	6.74	9.94	0.517%
2001	610	6,305,080	9.67	8.39	12.79	0.694%
2002	581	6,442,797	9.02	7.87	12.70	0.631%
2003	541	6,590,233	8.21	7.02	10.34	0.564%
2004	551	6,727,680	8.19	7.03	10.87	0.555%
2005	692	6,873,649	10.07	8.66	12.93	0.723%
2006	668	7,020,207	9.52	8.17	11.44	0.684%
2007	726	7,168,354	10.13	8.64	13.41	0.709%

* rates reported per 100,000 subjects

† standardized using the European standard population, Source: 1991 World Health Annual of Statistics - based on J Waterhouse et al, Cancer Incidence in Five Continents, Lyon, IARC, 1976 (Vol. 3, page 456)

Table II

Incidence of invasive melanoma

Year	Cases	Population in Catalonia	Crude Rate per 100,000	Age standardized rate ^{*,†}	Truncate rate* (35–64)	Cumulative rate (0–74)
2000	337	6.213.904	5.42	4.79	7.29	0.369%
2001	421	6.305.080	6.68	5.85	9.08	0.488%
2002	391	6.442.797	6.07	5.33	8.85	0.426%
2003	341	6.590.233	5.17	4.43	6.57	0.353%
2004	371	6.726.395	5.52	4.77	7.32	0.382%
2005	461	6.873.649	6.71	5.80	8.63	0.487%
2006	443	7.020.207	6.31	5.40	7.82	0.445%
2007	485	7.168.354	6.77	5.80	9.06	0.473%

* rates reported per 100,000 subjects

† standardized using the European standard population. Source: 1991 World Health Annual of Statistics - based on J Waterhouse et al. Cancer Incidence in Five Continents, Lyon, IARC, 1976 (Vol. 3, page 456)

Table III

Incidence by sex of invasive melanoma

Gender	year	cases	N Catalunya	Crude Rate*	Age standardized rate*†	Truncate rate* (35-64)	Cumulative rate (0-74)
Males	2000	175	3.037.429	5,76	5,10	7,22	0,399%
Males	2001	209	3.088.541	6,77	6,02	8,82	0,524%
Males	2002	215	3.164.113	6,79	6,10	9,15	0,484%
Males	2003	215	3.242.996	6,63	5,89	8,31	0,467%
Males	2004	190	3.316.066	5,73	5,04	7,48	0,399%
Males	2005	253	3.396.257	7,45	6,64	8,90	0,573%
Males	2006	241	3.473.240	6,94	5,98	7,56	0,497%
Males	2007	250	3.550.658	7,04	6,33	9,29	0,528%
Females	2000	220	3.176.475	6,93	6,14	9,41	0,465%
Females	2001	293	3.216.539	9,11	8,00	12,91	0,640%
Females	2002	243	3.278.684	7,41	6,44	10,97	0,526%
Females	2003	216	3.347.237	6,45	5,55	8,87	0,440%
Females	2004	244	3.410.329	7,15	6,09	9,59	0,487%
Females	2005	255	3.477.392	7,33	6,24	10,34	0,502%
Females	2006	265	3.546.967	7,47	6,47	10,29	0,523%
Females	2007	286	3.617.696	7,91	6,54	10,53	0,524%

* rates reported per 100,000 subjects

† standardized using the European standard population. Source: 1991 World Health Annual of Statistics - based on J Waterhouse et al. Cancer Incidence in Five Continents, Lyon, IARC, 1976 (Vol. 3, page 456)

Table IVa

Evolution of in situ/invasive melanomas distribution from 2000 to 2007

Year	Total	in situ	Invasive
2000	371	87	284
		23.50%	76.50%
2001	458	93	365
		20.30%	79.70%
2002	458	118	340
		25.80%	74.20%
2003	417	105	312
		25.20%	74.80%
2004	422	103	319
		24.40%	75.60%
2005	574	158	416
		27.50%	72.50%
2006	559	155	404
		27.70%	72.30%
2007	606	166	440
		27.40%	72.60%
Total	3865	985	2880
		25.50%	74.50%

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Table IVb

Evolution of Breslow thickness distribution from 2000 to 2007

Year	Total	0.1-1mm	1.1-2mm	2.1-4mm	>4mm
2000	304	165 54.30%	78 25.70%	30 9.90%	31 10.20%
2001	394	230 58.40%	76 19.30%	49 12.40%	39 9.90%
2002	370	200 54.10%	75 20.30%	51 13.80%	44 11.90%
2003	359	180 50.10%	72 20.10%	63 17.50%	44 12.30%
2004	344	178 51.70%	70 20.30%	56 16.30%	40 11.60%
2005	402	211 52.50%	87 21.60%	63 15.70%	41 10.20%
2006	411	211 51.30%	87 21.20%	61 14.80%	52 12.70%
2007	450	236 52.40%	95 21.10%	62 13.80%	57 12.70%
Total	3034	1611 53.10%	640 21.10%	435 14.30%	348 11.50%

Table V

Evolution of Mean Breslow thickness and Mean age of onset from 2000 to 2007

		Breslow	Age at diagnosis
2000	Mean	1.8229	53.07
	N	371	481
	sd	2.76132	18.769
2001	Mean	1.8875	53.98
	N	476	610
	sd	2.47813	16.994
2002	Mean	2.0606	56.04
	N	443	581
	sd	3.23201	17.155
2003	Mean	1.9878	55.12
	N	415	541
	sd	2.65989	17.853
2004	Mean	2.133	55.32
	N	430	551
	sd	2.96113	17.511
2005	Mean	1.8242	56.3
	N	485	692
	sd	2.23086	17.328
2006	Mean	2.114	57.24
	N	483	668
	sd	3.01731	17.455
2007	Mean	2.3162	58.27
	N	520	726
	sd	4.99593	16.935
Total	Mean	2.0242	55.84
	N	3629	4850
	sd	3.18929	17.512
p		0.222	0.000

Table VI

Breslow Thickness, Age at diagnosis and distribution of body site according to sex.

	Total	Men	Women	p
	Mean (sd)	Mean (sd)	Mean (sd)	
Breslow	2.02 (3.18)	2.28 (3.29)	1.80 (3.09)	0.000
Age at diagnosis	55.84 (17.51)	57.70 (16.90)	54.29 (17.84)	0.000
Body site				
Acral	388 (7.8%)	140 (6.3%)	248 (9%)	p<0.000
Lower Ext.	1004 (20.1%)	216 (9.7%)	779 (28.3%)	
Upper Ext.	584 (11.7%)	210 (9.5%)	369 (13.4%)	
Head and Neck	253 (5.1%)	158 (7.1%)	91 (3.3%)	
Face	571 (11.4%)	269 (12.1%)	300 (10.9%)	
Trunk	1876 (37.5%)	1083 (48.9%)	783 (28.5%)	
Mucosal	49 (1%)	14 (0.6%)	34 (1.2%)	
Other	200 (4%)	89 (4%)	108 (3.9%)	

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