European Journal of Cancer 41 (2005) 126–132

European Journal of Cancer

www.ejconline.com

Seasonal variation in the occurrence of cutaneous melanoma in Europe: influence of latitude. An analysis using the EUROCARE group of registries☆

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Received 4 May 2004; received in revised form 31 August 2004; accepted 8 September 2004
Available online 7 October 2004

Abstract

The aim of our study was to analyse seasonal variations in melanoma incidence in Europe. Data from 28 117 cutaneous melanoma cases reported during 1978–1993 to the EUROCARE group of registries were analysed. There is a clear summer peak in incidence in Western countries (summer–winter ratio: 1.31 $P < 0.0001$; Nam's test), which was not observed in Central Europe (ratio: 1.06; $P = 0.0699$). The amplitude of seasonality is higher for females (ratio = 1.38, 95% Confidence Interval (CI) [1.31–1.44]) than for males (ratio = 1.21 95%CI [1.14–1.29]). It is also higher for upper and lower limbs (1.44 and 1.46, respectively), than for head and neck or trunk regions (1.09 and 1.20, respectively). The amplitude of seasonality also varies with latitude and increases with time: in a linear regression adjusting for age, gender and anatomical localisation, the date of diagnosis was significantly closer to summer solstice with decreasing latitude ($P = 0.0005$) and for more recent year of diagnosis ($P = 0.0123$). The effect of latitude on the amplitude of the seasonal variation in melanoma incidence in Europe may be an indicator of ultraviolet B (UVB) exposure. Furthermore, an increase in intentional sun exposure could lead to an increase in melanoma promotion and thus to an increase in the amplitude of seasonal variation.

Keywords: Melanoma; Incidence; Season; Europe

☆ Mathieu Boniol was supported by a fellowship from Fondation de France. Esther de Vries was supported by the EORTC Melanoma group. EUROCARE was funded by the 3rd and 4th framework of the EC DG XII
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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.09.011

1. Introduction

The incidence of cutaneous melanoma is increasing steadily, doubling every 10–15 years [1]. An intriguing phenomenon is the existence of a seasonal variation in melanoma incidence with a summer peak [2–10]. This seasonality trend has been found in different parts of the world in registries and cancer surveys for cutaneous melanoma, but was never observed for ocular melanoma [4,11].

Some authors suggested that this increase of the incidence in the summer could derive from an over-diagnosis due to the efficacy of seasonal public campaigns and from a better awareness of the population or a better ability to detect a skin lesion when less clothes are worn during the summer time [6,10]. However, in the same way as the observation of a higher incidence of cutaneous melanoma, but not that of ocular melanoma [12], in southern latitudes [13–15], led to attribute a role in melanoma development to solar ultraviolet (UV) radiation, the seasonal variation in the incidence of cutaneous melanoma could also be due to a late promotion effect mediated by UV radiation [2,6,9].

Should the summer excess in the occurrence of cutaneous melanoma result from an increased ascertainment due to screening or higher awareness, then one would expect to observe melanomas diagnosed at an earlier stage. Moreover, this increased ascertainment in the summer months should be evidenced by an increase in the number of melanomas diagnosed on non-exposed body sites (such as the trunk). By contrast, if seasonal variation results from a late promotion effect, then one could think of a boosting of the last steps of melanoma progression leading to melanomas with a clinically more aggressive phenotype.

The significant seasonal variation in cutaneous melanoma incidence was observed for invasive melanomas, but not for *in situ* melanomas, which is in line with a late promotion effect [9]. Should the seasonal variation in melanoma incidence be the result of over-diagnosis in summer, then we should also observe a similar seasonal variation in the pre-invasive form of melanoma.

An effect of solar UV radiation on the seasonal variation in melanoma incidence was suspected based on the existence of a difference in the amplitude of seasonality according to latitude in the United States. The ratio of the number of summer–winter cases was higher in the South than in the North.

In Europe, the cancer registries participating in EUROCARE cover a large range of latitudes in Western and Central Europe [16]. In an analysis of melanoma characteristics in Europe, we observed higher incidence and lower Breslow thickness in Western than in Eastern Europe [17]. Using data from the same registries, we analysed the seasonal variation in melanoma incidence, the amplitude of seasonality according to the latitude and the characteristics of this seasonality according to host factors. We investigated the hypothesis of the existence of a difference in tumour progression stage according to the season of diagnosis, and explored in a multivariate analysis whether the period of diagnosis is stable over time.

2. Patients and methods

Data from the EUROCARE database were used for this analysis [16]. EUROCARE consists of routine population-based cancer registry incidence data, with a follow-up of 5 years. After exclusion of the Rotterdam registry (only one year of recording), data from 20 registries in 12 countries were used for this analysis. In some countries, the whole population was covered (Estonia, Slovenia, Slovakia, Sweden), in others, only regional registry data were available (France, Switzerland, the Netherlands, Poland, Spain, Italy, United Kingdom). The available data from the EUROCARE group were for the period of 1978–1993. However, some registries began to include observations in the EUROCARE project after 1978. Only invasive melanomas and cases with histological confirmation of the melanomas were included. In total 28 117 cases were included in the analyses, 22 659 from Western Europe and 5458 from Eastern Europe. In the database, both the ICD-9 and ICD-O-2 codings were used. When these codes did not match, we used the ICD-9 code, because this had been used before (16). Misclassifications due to these coding problems are not expected to be related to the season anyway.

Data analysis was performed using SAS software (SAS v8.2, SAS Institute Inc., Cary, NC, USA). Tests for seasonal variation in incidence were performed according to Nam's method [18], the ratio of summer–winter used the months of June–August for the summer and December–February for the winter.

The latitude chosen for each registry was of the city where the registry is situated to avoid a bias due to different catchment sizes. We used the Pearson's correlation test to assess the correlation between the latitude of registry and amplitude of the seasonality. Since Breslow's tumour thickness does not follow a normal distribution, we used the Kruskall–Wallis test to compare tumour thicknesses according to the season of diagnosis. Forty nine percent of the observations were excluded in the analysis of Breslow thickness due to missing values or non-reliable Breslow entries in the database (e.g., Breslow greater than 23 mm).

To analyse the independent effects of the different parameters in a multivariate analysis, we used the contribution of each case to the seasonality. This contribution was expressed as the distance in days between the date of diagnosis and the summer solstice (June 21st). Hence, each case was given an individual value for its period of diagnosis: the smaller the distance, the more this case contributed to seasonality. We analysed in a generalised linear model the effects of the latitude of the registry and of year of diagnosis on this distance between the date of diagnosis and the summer solstice, adjusting for age, gender and anatomical localisation. All analyses were based on a two-sided overall statistical significance level of 0.05.

3. Results

Table 1 shows that for most of the Western European registries, a significant seasonal variation existed in melanoma incidence during the period of 1978–1993, the summer–winter ratios varying from 1.10 (Stockholm) to 1.75 (Tarn). Two registries reported a limited number of cases or reporting cases over a shorter period of time. By contrast, there was no such seasonal variation in the Central Europe registries, except for Slovakia. Fig. 1 shows the number of cases diagnosed in Central and Western Europe by month of diagnosis, and indicates that the incidence of cutaneous melanoma peaks in June/July in Western Europe.

The amplitude of seasonal variation in melanoma incidence appeared to vary with the latitude of the registry (Table 1): it was higher for Southern countries than for Northern countries. Despite the small number of points available to calculate a relationship between the amplitude of the seasonality and latitude of the registry, the correlation is nearly significant $R = -0.4$, $P = 0.07$ Pearson's test (Fig. 2).

To evaluate an eventual effect of the season of diagnosis on the severity of the disease, we analysed the Breslow's tumour thickness according to the season of diagnosis in Western Europe (Table 2). The analysis used only the 11 598 melanoma cases for which a Breslow's thickness was available. Melanomas diagnosed in the winter were thicker than those in the summer (mean = 2.15 and 2.03 mm, respectively, and median = 1.5 and 1.5 mm, respectively, $P = 0.0027$; Kruskal–Wallis test), but this was mainly due to a higher proportion of few thick melanomas (>3 mm) diagnosed in the winter, whereas the proportion of thin melanomas (<0.5 mm) remained relatively stable throughout all seasons. By contrast, in Central Europe, where no seasonal variation was evidenced, no difference in Breslow's tumour thickness according to the season of diagnosis was observed (data not shown). Since there was a high proportion of missing values for Breslow thickness, we tested the seasonal variation of melanoma according to the presence or absence of information for Breslow thickness. No differences were observed in the frequencies of melanoma by month of diagnosis between cases with thickness information and cases without this information in the Western registries ($P = 0.58$; χ^2 test) or in the Eastern registries ($P = 0.60$; χ^2 test).

We further investigated the association between the main host characteristics (age, gender, anatomical localisation of the tumour) and season of diagnosis of melanoma. Age was not associated with the season of diagnosis (data not shown). However, the amplitude of

Table 1
Registries in EUROCARE: number of melanoma cases and amplitude of seasonality

Registry	Period	Number of cases	Latitude (°)	Summer–winter ratio	P value (Nam test of seasonality)
Western Europe		22659	–	1.31	<0.0001
East Anglia (United Kingdom)	1978–1992	2207	52.13	1.50	<0.0001
Eindhoven (Netherlands)	1978–1992	894	51.26	1.20	0.0281
Geneva (Switzerland)	1983–1991	449	46.12	1.34	0.0141
Granada (Spain)	1987–1992	175	37.10	1.38	0.0682
Lombardy (Italy)	1978–1992	649	45.28	1.45	0.0004
Lund (Sweden)	1991–1992	526	55.42	1.51	0.0005
Oxford (United Kingdom)	1978–1993	2644	51.44	1.16	0.0043
Saarland (Germany)	1978–1992	1080	49.14	1.33	0.0005
Stockholm (Sweden)	1978–1991	3102	59.30	1.10	0.0252
Tarn (France)	1982–1992	265	44.01	1.75	0.0007
Turin (Italy)	1985–1991	469	45.03	1.26	0.0384
Tuscany (Italy)	1985–1989	392	43.46	1.34	0.0199
Yorkshire (United Kingdom)	1978–1992	2892	53.58	1.25	<0.0001
Wessex (United Kingdom)	1978–1992	2734	51.04	1.55	<0.0001
West Midlands (United Kingdom)	1978–1992	4181	52.29	1.34	<0.0001
Central Europe		*5458*	–	1.06	0.0699
Krakow (Poland)	1978–1992	332	50.04	0.92	0.0699
Estonia (national registry)	1978–1992	876	59.00	0.84	0.9682
Slovakia (national registry)	1978–1990	2709	48.04	1.14	0.0097
Slovenia (national registry)	1983–1992	1061	46.03	1.12	0.0957
Warsaw (Poland)	1987–1992	480	52.16	1.06	0.3328

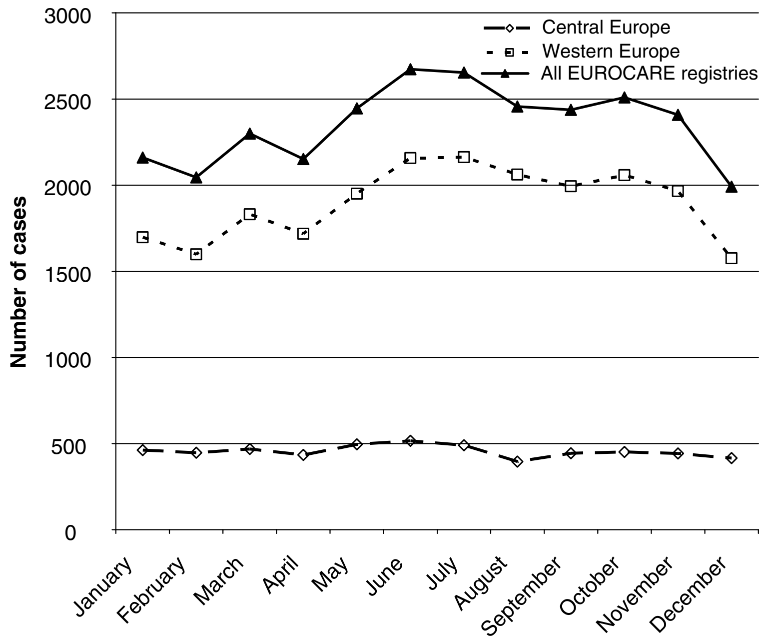

Fig. 1. Number of cases by month of diagnosis.

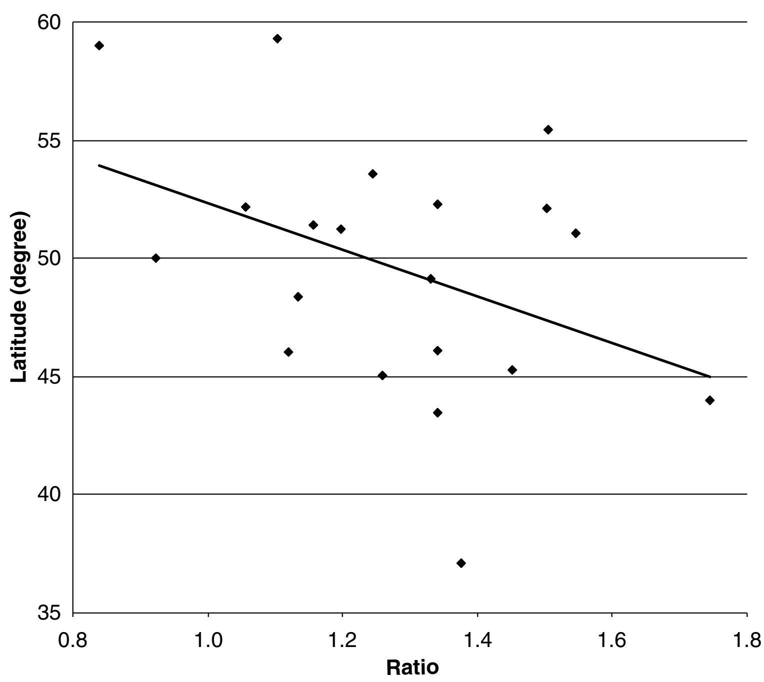

Fig. 2. Amplitude of the seasonal variation (ratio of number of cases summer–winter) of cutaneous melanoma according to latitude in EUROCARE.

seasonal variation varied with gender and the anatomical localisation of the tumour (Table 3). We observed only limited seasonality for head and neck melanomas, but an important seasonal variation for melanomas on the extremities and trunk. We also observed a difference between men and women: the amplitude was significantly greater for women than for men (the Confidence Intervals of summer–winter ratios did not overlap). This difference between males and females could not be attributed to a confounding effect of anatomical localisation, since in a stratified analysis the amplitude was always greater or equal in females than in males, independent of the anatomical site under study (data not shown).

Table 2
Breslow's tumour thickness (mm) of melanoma cases in Western Europe in EUROCARE study for the period of 1978–1993 according to the season of diagnosis

Season	*N*	Median	Inter-quartile range	Distribution of Breslow thickness by season (%)			
				⩽0.5 mm	[0.5–1.5 mm]	[1.5–3 mm]	>3 mm
Winter (December–February)	2430	1.5	[0.7–2.7]	17.5	35.6	27.7	19.1
Spring (March–May)	2817	1.3	[0.7–2.5]	18.4	39.1	24.4	18.1
Summer (June–August)	3242	1.5	[0.7–2.5]	17.7	36.6	28.8	16.8
Autumn (September–November)	3109	1.3	[0.7–2.5]	18.0	38.5	26.4	17.1

$P = 0.0027$ (Kruskall–Wallis test, $\chi^2 = 14.16$).

Table 3
Amplitude of seasonality in melanoma incidence according to anatomical localisation and gender

	Summer–winter ratio [95% CI]	
	Western Europe	Central Europe
Anatomical localisation		
Head and neck	1.09* [0.99–1.20]	1.07 [0.88–1.31]
Trunk	1.20** [1.12–1.29]	0.99 [0.87–1.12]
Upper limb	1.44** [1.32–1.58]	1.04 [0.85–1.27]
Lower limb	1.46** [1.38–1.56]	1.12 [0.97–1.28]
Other/unspecified	1.43* [1.03–1.99]	1.28 [0.92–1.78]
Sex		
Male	1.21** [1.14–1.29]	1.05 [0.94–1.18]
Female	1.38** [1.31–1.44]	1.06 [0.96–1.17]

Amplitude is the ratio of melanomas diagnosed in the summer to melanomas diagnosed in the winter; the 95% CI is derived from the Nam's test for seasonality.
95% CI, 95% Confidence Interval.
* $p < 0.05$.
** $p < 0.01$.

We used a generalised linear model to study the predictors of the distance in days between the date of diagnosis and the summer solstice (June 21) in Western Europe. This model also included the latitude of the registry and the year of diagnosis, and was adjusted for age, gender, and anatomical localisation of the tumour. Confirming the crude correlation observed between the latitude of the registry and amplitude of seasonal variation (Fig. 2), we found that latitude influenced the distance to solstice ($t = -3.51$, $P = 0.0005$): the more southern the domicile of a case, the closer was the date of diagnosis to the summer solstice.

In addition, the year of diagnosis was also related to this distance ($t = 2.50$, $P = 0.0123$), melanomas diagnosed in recent years being closer to the summer solstice. The period of diagnosis of cutaneous melanoma was thus not stable over time and a significant linear increase was exhibited in the amplitude of the seasonal variation over successive years in Western Europe.

4. Discussion

Our study, using the registries participating in this sub-study of the EUROCARE project, confirmed the presence of seasonal variation, with a summer peak in the incidence of cutaneous melanoma in Europe, as already described in different parts of the world, including some European countries. Interestingly, a significant seasonal variation was evidenced in all but one Western European registry, whereas this appeared in only 2 of the 5 registries from Central Europe, and with a much smaller amplitude and significance. One of the differences between Western and Central Europe is the later diagnosis of melanoma in the latter which was demonstrated in the same registries [17]. This delay in diagnosis in Central Europe may have led to a smoothing of the seasonal variation, rendering it undetectable.

In Western countries, where seasonal variation in melanoma incidence existed, seasonality of melanoma incidence was also affected by latitude which in turn affected the distance to solstice, both correlations being of borderline significance. The amplitude of seasonality in melanoma diagnosis was greater in states that are closer to the Equator [2]. This study could be the first demonstration of a direct link between the seasonality of melanoma diagnosis and the latitude of residence. This observation is in line with the hypothesis of a role of ultraviolet radiation as a promoting factor of the progression of melanoma during the late stages of development of the disease.

However, we did not observe that melanoma would be diagnosed in a more advanced stage (as determined with Breslow's tumour thickness) in the summer than in the winter. On the contrary, we found a reverse association, which actually resulted from a few thick melanomas diagnosed in winter; the clinical difference according to season was not relevant (for the mean or median).

One could suggest that this result is in line with the hypothesis of melanomas diagnosed in summer being at an earlier stage due to an overdiagnosis during this period. But the result itself is questionable since we had to exclude 49% of observations. Some registries did not record Breslow's thickness, but for those who normally recorded thickness, the exclusions due to missing values for Breslow's thickness were not randomly distributed: missing values occurred more frequently for registries of Central and Southern Europe, with increasing age at diagnosis and for women. Furthermore, the distribution of the Breslow's thickness in the remaining observations was far from a linear one as we found some highly repeated values (1, 1.5, 2) in our dataset. These problems illustrate the heterogeneity in data collection and coding across registries; 5 out of 21 registries did not register Breslow's tumour thickness. There is no reason why the distribution of Breslow's thickness would not be linear when the diagnostic process is homogeneous [19].

In the United States [6], the amplitude of seasonal variation was higher for women than for men. This difference could result from a better skin awareness of women resulting in an increase in the number of melanomas diagnosed in the summer for women. However, as women are more willing to get a tan and tend to sunbathe more than men, this difference in amplitude could also be due to a promoting effect of UV exposure that is greater for women than for men.

The existence of seasonal variations in melanoma incidence has also been attributed to seasonal variations in clothing habits. Further, our observation that the amplitude of seasonality is greater for melanomas on the extremities than for head and neck melanomas could result from seasonal variations in clothing habits. However, if seasonality in the incidence of cutaneous melanoma stems from variations in clothing habits, then we would expect to observe a seasonal variation of even greater amplitude for melanomas developing on usually non-exposed body sites (such as the trunk). But the amplitude of seasonal variation is lower for the trunk than for the extremities. The difference in amplitude of seasonality between different body sites could reveal that some body sites are actually more sensitive to a promoting effect of recent exposure.

The observed increases in amplitude of seasonality in melanoma incidence with a more recent year of diagnosis may reveal that melanomas are more and more frequently diagnosed close to the summer solstice. The important increases in the incidence of cutaneous melanoma during the past half century has been mainly attributed to a continuous temporal change in sun exposure habits, but this does not preclude a promotion effect on the late stages of melanoma development.

Most secondary prevention campaigns were only implemented in the late 1980s in Northern and Western Europe, but as there were set up slowly they are unlikely to have affected the amplitude of seasonal variation in the period used in our analysis. The continuous temporal change of the amplitude of the seasonal variation is more in line with a promoting effect of UV exposure and could be related to a change in behaviour with an increased intentional sun exposure, and possible increases in global UV irradiation.

The association between latitude and amplitude of the seasonal variation in melanoma incidence is also more in line with this hypothesis. In Western Europe with its North to South gradient of intentional sun exposure (Northern inhabitants are more willing to get a tan despite of their pale complexion), recent exposure to UV light could have a promoting effect on the development of melanoma.

Biological studies confirm the existence of a short-term effect of UV irradiation for promoting the growth of naevi or melanoma. After a short period (14 days) of intense exposure, naevi components changed and some of them acquired dysplastic features [20]. The existence of a seasonal variation in DNA damage in peripheral blood lymphocytes measured by the COMET assay showed the rapid deleterious effect of recent solar exposure [21]. Further, UVB irradiation of melanoma cell lines triggered their metastatic ability [22].

Finally, the association between seasonal variation in melanoma incidence and decreasing latitude of residency would add further support to the involvement of exposure to UVB in melanoma occurrence and progression, which is currently supported by biological and epidemiological data [23,24]. UVB radiation appears to be a better candidate than UVA of such a promoting effect since the increases in the proportion of UVB in solar radiation with decreasing latitude are more pronounced than those of UVA [25,26].

Our study points to the possible influence of recent exposure as a promoting effect on melanoma development, as was suspected by the observed seasonal variation in incidence. However, the observation of a higher amplitude of seasonality for women and for extremities could also indicate a role of better ascertainment during the summer (due to less clothing worn or sensitising to harmless visible effect of solar exposure such as sunburns, skin color changes, freckles development, lentigines development) which leads to a rise in melanoma excisions in the summer. The two possible hypotheses to explain the seasonal variation of melanoma incidence could coexist and explain the different characteristics of seasonality we evidenced in our study.

An analysis of seasonality in melanoma incidence in Europe may help in gaining insight into the mechanisms of melanoma development in relation to UV exposure, and the influence of latitude may indicate a role for UVB.

Acknowledgement

The authors wish to gratefully acknowledge Pr. Alexander MM Eggermont, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, for his supportive interest in this project and Dr. Philippe Autier, for helpful discussions.

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