 DOI 10.1111/j.1365-2133.2007.08029.x

Trends in melanoma epidemiology suggest three different types of melanoma

D. Lipsker, F. Engel, B. Cribier, M. Velten* and G. Hedelin*

*Clinique Dermatologique and *Laboratoire d'Epidémiologie des Hôpitaux Universitaires de Strasbourg, Faculté de Médecine, Université Louis Pasteur, 1 place de l'hôpital, F-67091 Strasbourg cedex, France*

Correspondence
Dan Lipsker.
E-mail: dlipsker@noos.fr

Accepted for publication
15 February 2007

Key words
Breslow thickness, early detection, epidemiology, melanoma, tumour growth

Conflicts of interest
None declared.

Summary

Background It has been suggested that the incidence of thin melanomas but not of thick tumours is rising in fair-skinned populations, although the reason for this discrepancy is not understood.

Objectives To describe temporal trends in melanoma epidemiology in a limited part of France in order to confirm this observation and to provide an explanation.

Methods This is a retrospective population- and academic centre-based study in which all melanomas diagnosed in the department of the Bas-Rhin, France between January 1980 and December 2004 were included.

Results The study included 2094 melanomas diagnosed in 2020 patients. There was a steady increase in incidence of thin (< 1 mm) melanomas, mainly located on the trunk, and to a lesser extent in the head and neck region, in both sexes, and of intermediate (1–2 mm) melanomas in men. The incidence of intermediate melanomas in women and of thick (> 2 mm) melanomas, as well as mortality related to melanoma, remained stable. There was a steady decline of mean and median Breslow thickness. The 12 months median delay to diagnosis of thick tumours was significantly shorter than the 24 months delay to diagnosis of thin tumours.

Conclusions Temporal trends suggest the existence of three unrelated types of melanoma: type I, thick melanomas, with stable incidence; type II, thin melanoma with a steady and important increase in incidence, mainly located on the trunk; and type III, melanoma with a slower increase in incidence, mainly located on the head and neck region.

Melanoma incidence is rising in most countries of the Western world.[1–12] A part of this increasing incidence is attributable to better and earlier detection of melanoma, due to a greater knowledge of the disease by patients and physicians.[13–15] Another significant part of this rise in incidence is related to a change in sun-exposure behaviour, as more and more people are exposed to natural and/or artificial ultraviolet radiation, a known risk factor for melanoma, in the wish to tan.[16,17] However, the rise in incidence is not homogeneous. Some years ago, we and others showed that the rise in incidence is mainly attributable to thin melanomas, while the number of intermediate or thick melanomas was stable.[18–21] Furthermore, there is no correlation between the magnitude of the rise in incidence of melanoma and the much lower rise or even stability of mortality related to melanoma.[8,10,18] We therefore suggested that two different epidemiological types of melanoma with different risk factors might exist. We have now performed an extensive study of melanoma epidemiology in a limited geographical area of France that was not subject to important migration over a 25-year period. We extend our previous findings and suggest the existence of three unrelated types of melanomas: (i) a slowly growing form of melanoma located on intermittently sun-exposed areas, with a sharply rising incidence, accessible to early detection; (ii) a very slowly growing form of melanoma located on permanently sun-exposed areas, with a moderate increase in incidence, accessible to early detection; and (iii) a fast-growing form of melanoma, that can arise on any part of the body but with a predilection on permanently sun-exposed areas, with a stable incidence, but which is responsible of the majority of deaths attributable to melanoma.

This model seems the best to date to explain our knowledge of melanoma epidemiology and biology.

Materials and methods

This study describes the temporal evolution of epidemiology of cutaneous melanoma in the department of the Bas-Rhin, France. All melanomas recorded in the population-based cancer registry

of the Bas-Rhin (Registre des cancers du Bas-Rhin) between January 1980 and December 2001 were included. Investigators from the registry conduct a survey each year in all private and public pathology laboratories and record every new case of melanoma. The data recorded include: year of diagnosis, sex and age of the patient. Data on mortality related to melanoma in the department of the Bas-Rhin were available for the period 1980–1999 through exhaustive reviewing of death certificates.

Seventy-two per cent of the melanomas were diagnosed in a single pathology centre, the Department for Cutaneous Histopathology, University Hospital, Strasbourg. In this laboratory, the diagnosis of melanoma was confirmed in all cases by two dermatopathologists. The melanomas diagnosed in this centre were submitted to further analysis, including: anatomical site, histopathology, tumour thickness, Clark level and the delay in diagnosis of melanoma, which was defined as follows: (i) for a newly appearing lesion, the length of time from the moment the patient had first noticed an abnormal lesion to the date of excision of the lesion; (ii) for pre-existing lesions, which had to be unchanged for 5 years at least, the length of time between the first clinical changes the patient noticed and excision. This information was obtained by personal interview of the patient. This detailed analysis also included the period January 2001–December 2004 which was not recorded in the cancer registry at the time of the present study.

Linear regression and χ^2 tests were applied where appropriate, using Statistica 6 (Statsoft, Tulsa, OK, U.S.A.). World standardized incidence rates were estimated using CanReg4 (International Agency for Research on Cancer, Lyon, France).

Results

Global epidemiology of melanoma in the department of the Bas-Rhin, 1980–2001 (data from the cancer registry of the department of the Bas-Rhin)

The annual melanoma incidence rate, adjusted for age to the local standard population, increased in both women and men during the reference period. In women, world-standardized incidence increased from 4·2/100 000 in 1980 to 13/100 000 in 2001 and in men from 2·3/100 000 to 10·2/100 000 (Fig. 1). The highest standardized incidence rates were 14·9/100 000 for women in 1999 and 15·5/100 000 for men in 2000.

The annual mortality rate related to melanoma in the same period ranged from 1·2/100 000 to 1·8/100 000 in men ($P = 0·12$) and from 1·6/100 000 to 0·9/100 000 in women ($P = 0·74$). There was no significant increase in mortality during the study period (Fig. 2).

Detailed analysis of melanomas diagnosed at the Department for Cutaneous Histopathology, University Hospital, Strasbourg between 1980 and 2004

Data included in this analysis also include the melanomas diagnosed between 2001 and 2004, which were not yet exhaustively recorded in the cancer registry data bank.

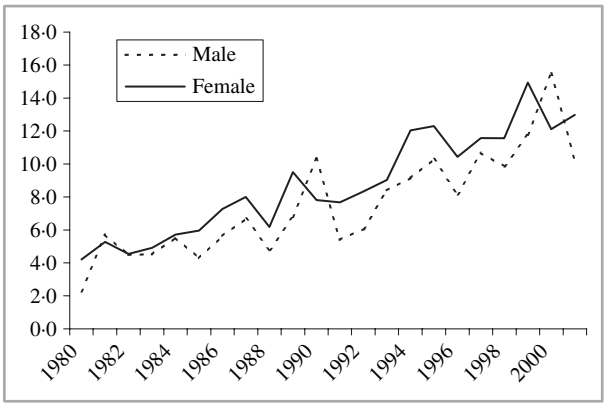

Fig 1. World-standardized incidence (values per 100 000 population) of melanoma in the department of the Bas-Rhin.

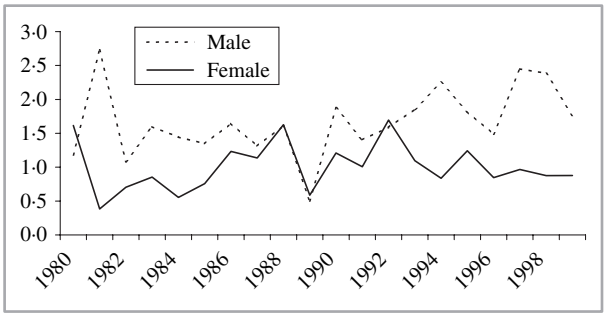

Fig 2. World-standardized mortality related to melanoma in the department of the Bas-Rhin (values per 100 000 population).

During the reference period, 2094 melanomas were diagnosed in 2020 patients. Sixty-four patients had more than one melanoma. There were 1138 women and 882 men (ratio F/M = 1·3) of mean age 55·7 years. The number of melanomas diagnosed each year in this laboratory increased in both men and women during the study period. Tumour thickness was available in 1657 cases. The mean and median tumour thicknesses were, respectively, 1·33 mm and 0·72 mm. Mean and median tumour thicknesses decreased steadily in both sexes between 1980 and 2004 (Fig. 3). Clark level was known for 1800 melanomas: 354 (19·7%) were

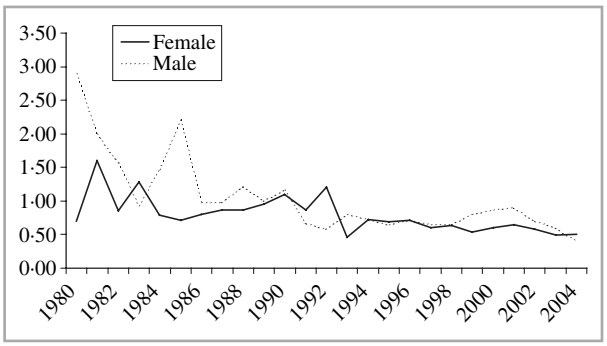

Fig 3. Tumour size as determined by median Breslow thickness.

Table 1 Distribution of melanomas according to sex

Site	Women	Men	Total
Head and neck			
Scalp	5	17	22
Face	243	140	383
Neck	28	34	62
Total	276	191	467
Trunk			
Thorax	42	82	124
Abdomen	26	52	78
Back	158	314	472
Total	226	448	674
Upper limb			
Upper arm	116	62	178
Forearm	47	31	78
Hand	27	16	43
Total	190	109	299
Lower limb			
Thigh	80	49	129
Leg	282	63	345
Foot	84	42	126
Total	446	154	600
Genital region			
Total	5	3	8
Unknown	29	17	46
Total	1172	922	2094

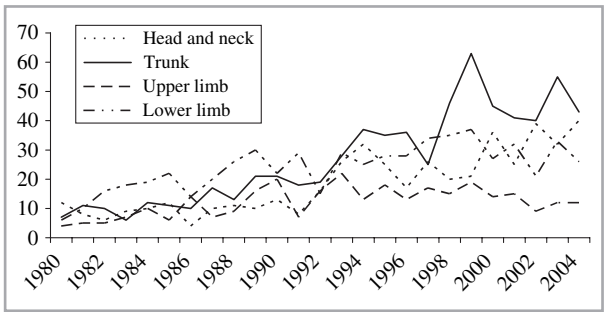

Fig 4. Temporal evolution of melanoma localization.

in situ Clark level I, 430 (23·9%) were Clark level II, 548 (30·4%) were Clark level III, 402 (22·3%) were Clark level IV and 66 (3·7%) were Clark level V. Table 1 shows the anatomical site of the melanomas according to sex. Melanomas were mostly located on the trunk in men (48·6% vs. 19·3% in women) and lower limbs in women (38·1% vs. 16·7% in men). There were, however, significant time trends in the distribution of anatomical sites of melanomas (Fig. 4). Indeed, there was a significant increase in melanomas of the trunk in both sexes ($P < 0·001$). In women, we observed an increase in melanomas on the trunk (from 11·4% in 1980–84 to 22·8% in 2000–04) and a decrease in melanomas on the lower limbs (from 45·5% in 1980–84 to 32·9% in 2000–04). Furthermore, we observed a regular increase in melanoma in the head and neck region in both sexes. The growth pattern

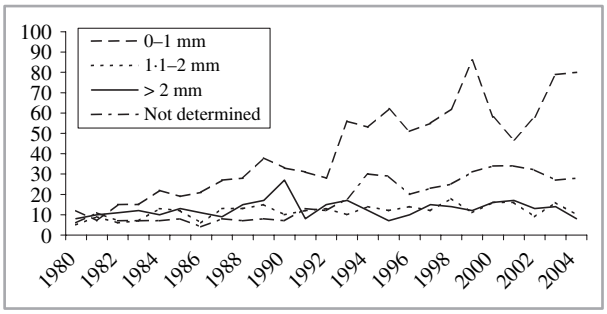

Fig 5. New cases of melanoma according to tumour thickness.

was known in 1829 cases. There were 1007 (55·1%) superficial spreading melanomas, 363 (19·8%) nodular melanomas, 354 (19·4%) lentigo maligna melanomas and 105 (5·7%) acrolentiginous melanomas.

There were striking differences in the temporal evolution of melanoma incidence according to tumour thickness (Fig. 5). The number of thin melanomas (< 1 mm) increased dramatically in both sexes ($P < 0·001$). The number of intermediate melanomas (1–2 mm) increased slightly in men ($P < 0·001$), but remained stable in women ($P = 0·89$). The number of melanomas with a Breslow thickness > 2 mm was stable in both sexes ($P = 0·69$ in women and $P = 0·75$ in men for melanomas between 2 and 4 mm, and $P = 0·75$ in women and $P = 0·18$ in men for melanomas > 4 mm).

We compared patients with thin melanomas (< 1 mm) with those with thick melanomas (> 2 mm). There was no statistical difference in the number of melanomas arising *de novo* or on a pre-existing naevus. However, thick tumours were significantly more frequent in men and in the elderly (> 60 years).

The delay in the diagnosis of melanoma was known in 717 patients. The mean and median values were, respectively, 44 and 24 months. This delay was significantly shorter in thick (> 2 mm) melanomas (mean 25 months, median 12 months) than in thin (< 1 mm) melanomas (mean 54 months, median 24 months) ($P < 0·001$). When we compared the patients with a short delay to diagnosis (≤ 12 months) with those with a long delay (≥ 24 months), only tumour thickness was significantly greater in patients in whom melanomas were rapidly excised. There was no statistically significant difference in regard to sex ratio ($F/M = 1·3$), mean age (56·2 years in both groups) or age distribution (≤ 20, 21–40, 41–60, 61–80 and > 80 years). There was also no difference in regard to number of melanomas appearing *de novo* or on a pre-existing naevus.

There was no significant difference in regard to F/M ratio, mean age or mean tumour thickness between the groups of patients in whom information about the delay to diagnosis was available when compared with the rest of the study population. There were also no statistical differences in the distribution of age (≤ 20, 21–40, 41–60, 61–80 and > 80 years) or the distribution of tumour thickness (< 1, 1–2, 2·01–4 and > 4 mm) between the two groups.

Discussion

In this study we show a steady increase in incidence of thin melanomas that contrasts (i) with a stable incidence of thick melanomas and (ii) with the stability of melanoma mortality over a 25-year period. Furthermore, we found that the delay to diagnosis was shorter in thick tumours.

The 12/100 000 melanoma incidence rate in the Bas-Rhin department is close to the incidence rates in other central European countries.[1–3,8–10] Although every thick melanoma starts thin, the data we show here support the notion that, at least from an epidemiological point of view, there are three different and unrelated tumour types. The first group comprises thick melanomas or type I melanoma, the incidence of which is stable in time. It is under-represented on the trunk, normally distributed on the limbs and in excess on the head and neck region. This distribution does not support intermittent sun exposure as being a risk factor for this type of melanoma. The second group comprises melanomas mainly located on the intermittently sun-exposed skin of the trunk and limbs of middle-aged people (type II melanoma). In this group, it is of interest that the classic distinction of melanoma occurring on the legs in women and on the back in men tends to vanish from the 1990s onwards. Indeed, the trunk is becoming the first site of melanoma in both sexes. This is probably the consequence of sun-exposure habits. The third group comprises melanomas occurring on continuously sun-exposed skin of the head and neck region of older people (type III melanoma). Increase in this group is probably the result of an ageing population.

These epidemiological differences do not, however, merely illustrate the different histogenetic types of melanoma. The classification of melanoma into the four classical histogenetic types is currently subject to debate[22] and is less frequently used, also in our laboratory, especially as it bears no prognostic information.[23,24] Some studies at the molecular level corroborate this classification. Indeed, mutations in *BRAF* are the most frequent mutations occurring in human melanomas and naevi.[25–27] Yet *BRAF* mutations are mainly found in melanomas arising on skin intermittently exposed to the sun (type II melanoma), but much less often on melanomas in sun-protected or continuously sun-exposed sites.[25,26] Furthermore, Berwick and her group showed that a history of sunburn, high intermittent sun exposure and, histologically, the presence of solar elastosis, a marker of sun damage, confer better prognosis to melanoma.[28] As all those markers are related to sun exposure, which is necessary for the synthesis of vitamin D_3, those authors hypothesized that one possible explanation might be that vitamin D_3 could have a protective effect. However, these three features could simply be the surrogate for a special type of melanoma bearing an overall better prognosis, namely the intermittently sun-exposed type of melanoma, or type II melanoma, which usually displays *BRAF* mutations, and which is responsible for what some called the 'epidemic' increase in melanoma incidence.[29]

The strong increase in thin tumours has resulted in a decrease of the median Breslow thickness, with a median value of about 0·5 mm by the end of the 1990s, a value close to what has been observed in Queensland, Australia since the 1980s.[8] A decrease in median Breslow thickness is reported in most occidental countries, the decrease being the most significant in the countries with the greatest incidence rates.[30] However, neither the number of thick tumours nor melanoma-related mortality significantly decreased during the 25-year period. Furthermore, we found that the delay to diagnosis was significantly shorter in thick (> 2 mm) tumours compared with thin tumours (< 1 mm) with a median delay

Table 2 Classification of melanoma in three subtypes based on clinical, biological and epidemiological findings according to Lipsker[35]

	Type I melanoma	Type II melanoma	Type III melanoma
Growth rate	Fast	Slow	Slow
Incidence	Stable	Increasing[a]	Increasing[b]
BRAF mutations	Absent[c]	Present	Absent
Prognosis	Bad	Good	Good
Possibility of early detection and prevention	No	Yes	Yes
Role of sun exposure in melanoma genesis	? Probably not	Yes, intermittent sun exposure	Yes, continuous sun exposure
Localization	Random? Must still be assessed precisely	Intermittently sun-exposed body parts, mainly the trunk	Continuously sun-exposed body parts, mainly the head and neck region
Clinical characteristics	Fast growing, often amelanotic nodule. Clinical appearance of very early lesions unknown	ABCDE	ABCDE

[a]Important increase, probably related to intermittent sun exposure; [b]moderate increase, probably related to continuous sun exposure of an ageing population; [c]absence of *BRAF* mutations is a hypothesis and has still to be proven. ?, Unknown.

of, respectively, 12 vs. 24 months. This has previously been observed by us and by others.[18,31,32] Unfortunately, these data were based on a sample of 717 lesions out of a total of 2094 melanomas. This huge loss of information might affect the validity of the proposed model. However, when we compared the group of patients in whom the information was provided with those in whom it was not, we found no statistically significant difference in regard to sex distribution, age distribution or mean tumour thickness. Therefore, we think that the information is still valid.

A recent work by Liu *et al.*[33] sheds some light on these intriguing observations by showing that about one-third of melanomas are fast-growing tumours with an increase of tumour thickness of more than 0·5 mm per month. This group also showed that those lesions occur mainly in the elderly as symmetrical and often amelanotic lesions. Thus, those lesions are difficult to diagnose clinically and only the recently added 'E' criterion of the 'ABCD' rule for early detection of melanoma applies to those tumours.[34] These lesions are the paradigm of type I melanomas. This variability in melanoma growth rate probably explains the stability of thick tumours and melanoma-related mortality. Indeed, those biologically aggressive type I melanomas seem not to be sun induced. Due to their rapid growth rate, they are not accessible to early detection. Thus, neither a change in sun-exposure behaviour nor early detection campaigns influence their number. In contrast, type II and type III melanomas are sun related and accessible to early detection. These are the reasons why we recently suggested classifying melanoma in three subtypes as shown in Table 2.[35] The challenge in the coming years will be to identify the risk factors and early clinical features of the fast-growing type I melanomas.

References

1 Marks R. Epidemiology of melanoma. *Clin Exp Dermatol* 2000; **25**:459–63.
2 Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol* 2002; **146**:1–6.
3 Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet* 2005; **365**:687–701.
4 Bevona C, Sober AJ. Melanoma incidence trends. *Dermatol Clin* 2002; **20**:589–95.
5 Jemal A, Devesa SS, Hartge P, Tucker MA. Recent trends in melanoma incidence among whites in the United States. *J Natl Cancer Inst* 2001; **93**:678–83.
6 Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol* 1999; **40**:35–42.
7 Marrett LD, Nguyen HL, Armstrong BK. Trends in the incidence of cutaneous malignant melanoma in New South Wales, 1983–1996. *Int J Cancer* 2001; **92**:457–62.
8 Garbe C, Roderick G, McLeod C, Buettner PG. Time trends of cutaneous melanoma in Queensland, Australia and central Europe. *Cancer* 2000; **89**:1269–78.
9 de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in Western Europe and decreases in Scandinavia. *Int J Cancer* 2003; **107**:119–26.
10 MacKie RM, Bray CA, Hole DJ *et al.* Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. *Lancet* 2002; **360**:587–91.
11 van der Rhee HJ, van der Spek-Keijser LMT, van Westering R, Coebergh JWW. Increase in and stabilization of incidence and mortality of primary cutaneous malignant melanoma in western Netherlands, 1980–95. *Br J Dermatol* 1999; **140**:463–7.
12 Herd RM, Cooper EJ, Hunter JAA *et al.* Cutaneous malignant melanoma: publicity, screening clinics and survival: the Edinburgh experience 1982–90. *Br J Dermatol* 1995; **132**:563–70.
13 MacKie RM, Hole D. Audit of public health campaign to encourage earlier detection of malignant melanoma. *BMJ* 1992; **304**:1012–15.
14 Melia J, Cooper EJ, Frost T *et al.* Cancer research campaign health education programme to promote the early detection of cutaneous malignant melanoma. I. Workload and referral patterns. *Br J Dermatol* 1995; **132**:405–13.
15 Melia J, Cooper EJ, Frost T *et al.* Cancer research campaign health education programme to promote the early detection of cutaneous malignant melanoma. II. Characteristics and incidence of melanoma. *Br J Dermatol* 1995; **132**:414–21.
16 Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 1997; **73**:198–203.
17 Veierod MB, Weiderpass E, Thorn M *et al.* A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2003; **95**:1530–8.
18 Lipsker D, Hedelin G, Heid E *et al.* Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. *Arch Dermatol* 1999; **135**:1451–6.
19 Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States. *Arch Dermatol* 2005; **141**:745–50.
20 McMullen EA, Kee F, Patterson CC *et al.* Improved survival for melanoma in Northern Ireland: a comparison of two 5-year periods (1984–88 and 1994–98). *Br J Dermatol* 2004; **151**:587–93.
21 Weatherhead SC, Lawrence CM. Melanoma screening clinics: are we detecting more melanomas or reassuring the worried well? *Br J Dermatol* 2006; **154**:539–41.
22 Ackerman AN. Malignant melanoma. A unifying concept. *Hum Pathol* 1980; **11**:591–5.
23 Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. *Cancer* 1996; **78**:427–32.
24 Balch CM. Cutaneous melanoma: prognosis and treatment results world-wide. *Semin Surg Oncol* 1992; **8**:400–14.
25 Maldonado JL, Fridlyand J, Patel H *et al.* Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst* 2003; **95**:1878–90.
26 Curtin JA, Fridlyand J, Kageshita T *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; **353**:2135–47.
27 Kumar R, Angelini S, Snellman E, Hemminki K. BRAF mutations are common somatic events in melanocytic nevi. *J Invest Dermatol* 2004; **122**:342–8.
28 Berwick M, Armstrong B, Ben-Porat L *et al.* Sun exposure and mortality rate from melanoma. *J Natl Cancer Inst* 2005; **97**:1995–9.
29 Florez A, Cruces M. Melanoma epidemic: true or false? *Int J Dermatol* 2004; **43**:405–7.
30 de Vries E, Boniol M, Doré JF, Coebergh JWW. Lower incidence rates but thicker melanomas in Eastern Europe before 1992: a comparison with Western Europe. *Eur J Cancer* 2004; **40**:1045–52.

31 Richard MA, Grob JJ, Avril MF *et al.* Melanoma and tumor thickness. Challenges of early diagnosis. *Arch Dermatol* 1999; **135**:269–74.
32 Helsing P, Faye R, Langmark F. Cutaneous malignant melanoma: correlation between tumor characteristics and diagnostic delay in Norwegian patients. *Eur J Dermatol* 1997; **7**:359–61.
33 Liu W, Dowling JP, Murray WK *et al.* Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Arch Dermatol* 2006; **142**:1551–8.
34 Abbasi NH, Shaw HM, Rigel DS *et al.* Early diagnosis of cutaneous melanoma. Revisiting the ABCD criteria. *JAMA* 2004; **292**:2771–6.
35 Lipsker D. Growth rate, early detection and prevention of melanoma. The melanoma epidemiology revisited and challenges for the future. *Arch Dermatol* 2006; **142**:1638–40.