Acta Derm Venereol 2011; 91: 499–503

REVIEW ARTICLE

Are All Melanomas Dangerous?

Carsten NØRGAARD[1], Martin GLUD[1] and Robert GNIADECKI[1,2]
[1]Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark, and [2]Faculty of Health Sciences, University of Copenhagen, Denmark

The increased incidence of cutaneous malignant melanoma, together with only minor changes in mortality, has brought into question the existence of a melanoma epidemic. The discrepancy between incidence and mortality suggests that most newly diagnosed melanomas have indolent behaviour. This review summarizes the most recent epidemiological findings regarding the incidence of cutaneous malignant melanoma, mortality, Breslow thickness and clinical stage. Studies published between 2005 and 2010 with more than 2,000 test subjects were included in this review. These studies all report an increase in incidence of melanoma during the last few decades, with by far the highest increase in tumours at a very early stage (T1 or IA). Little or no change was seen in mortality. However, increases in both mortality and incidence of thick melanomas were found in the oldest subgroups, especially in men. These findings indicate the existence of a certain degree of overdiagnosis of melanoma. They also indicate the existence of two different types of epidemic, for younger and older subgroups. ***Key words: melanoma; incidence; mortality; thickness.***

(Accepted April 21, 2011.)

Acta Derm Venereol 2011; 91: 499–503.

Martin Glud, Department of Dermatology, Bispebjerg Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark. E-mail: glud.martin@gmail.com

Over recent decades there has been a massive increase in the reported incidence of cutaneous malignant melanoma (CMM) in white populations worldwide (1). The question as to whether this reflects a true melanoma epidemic is controversial (2–5). Several arguments against an epidemic have been proposed, the main one being that the majority of newly diagnosed melanomas represent very early grades of the disease, with only minor changes in the mortality rate. This inconsistency could be a result of a diagnostic drift, whereby lesions previously diagnosed as benign or borderline are reclassified as early CMM (3).

Another possible reason for the increase in reported melanomas is the increased level of scrutiny and diagnostic screening, resulting in the removal of larger numbers of lesions that are slow-growing and/or biologically benign (6). Finally, the increase has been attributed to an artefact of error amplification, whereby a diagnostic error of the earliest malignant melanomas leads to overdiagnosis (7). An interesting explanation for the apparent lack of increase in mortality is that many thin CMM would never progress if left untreated, or would progress at such a slow rate that the patient will not develop metastatic disease in his or her lifetime (5, 7, 8). The question about the overdiagnosis of cancer is not restricted only to CMM, but applies also to other neoplasms in which increasing tumour incidence is not matched by an increase in mortality (e.g. lung cancer, thyroid cancer and prostate cancer) (5). The aim of this paper is to review recent epidemiological findings of the incidence of, and mortality from, CMM, with a particular focus on the possibility that CMM tends to be overdiagnosed.

METHODS

We selected studies published between 2005 and 2010 that included more than 2,000 test subjects, and that reported incidence trends for a period of 10 years or more. The PubMed database was searched for articles, using the following search terms: primary/cutaneous melanoma/death/mortality/incidence/thickness/stage. Both single terms and combinations of term were used. Data about the number of patients of each sex, change in incidence, mortality, Breslow thickness and stage were extracted. With these inclusion criteria, eight articles were selected for this review (9–17). One article referred to a further article for data material and methods (12, 13).

RESULTS

Incidence and mortality

Table I lists all articles selected, with study-period, number of cases, country/region and change in mortality, incidence and Breslow thickness/TNM stage. All of the articles examined change in incidence, and all but one (9) found a significant increase in incidence. Furthermore, all except one (11) differentiated between men and women, and all found a significant increase in incidence for both sexes. Out of the eight articles, all but one (9) studied mortality, and all found a lower, or non-significant, increase in mortality than in incidence.

Changes in incidence and mortality are shown in Fig. 1a and b, respectively. These graphs are a function of only two points (the start- and end-point). Interestingly, the increase in incidence does not appear to be constant. For example, Metelitsa et al. (9) found no change in incidence during the period examined (1993–2002),

Table I. *Overview of selected published studies included in this review. Study period, number of cases, country/region and change in mortality, incidence and Breslow thickness/TNM stage are shown*

		Number of cases		Change in incidence		Change in mortality		Change in Breslow thickness/stage			
Study	Period	Men	Women	Men	Women	Men	Women	Men	Women	Area	Comments
Metelitsa et al. (9)	1993–2002	1,718	1,761	NSC		–		–		Alberta, Canada	
Linos et al. (10)	1992–2004	70,596		3.1% APC, 45% (18.2–26.3)[a]		0.4% APC		< 1 mm: 4.84% APC 1.01–2 mm: 2.39% APC 2.01–4 mm: 2.54% APC > 4.01 mm: 4.10% APC	< 1 mm: 4.68% APC 1.01–2 mm: 3.16% APC 2.01–4 mm: NSC >4.01 mm: 3.3% APC	USA	
				2.96% APC	3.21% APC	0.6% APC	NSC				
Levell et al. (11)	1991–2004	3,971		48% (9.39–13.91)		18% (2.16–2.54)		TNM 1: 87% TNM 2: 30% TNM 3: NSC TNM 4: –70%		Eastern UK	
Tryggvadóttir et al. (12)	1964–2003	10,383	13,972	410% (2.7–13.8)	270% (4.6–17.0)	100% (1.4–2.8)	120% (0.9–2.0)	–		Denmark	Most numbers regarding change in incidence and mortality are not shown in the text and have been extracted from graphs in the article (only 0.1 difference compared with the few numbers given).
		7,441	7,997	250% (2.6–9.0)	210% (2.5–7.8)	80% (1.2–2.2)	11% (0.9–1.0)	–		Finland	
		254	460	990% (1.1–12.0)	890% (2.0–19.8)	400% (0.4–2.0)	70% (0.7–1.2)	–		Iceland	
		11,327	13,260	300% (3.6–14.5)	280% (4.2–15.8)	130% (1.7–3.9)	130 % (1.1–2.5)	–		Norway	
		20,420	21,686	290% (3.2–12.5)	250% (3.7–13.0)	100% (1.4–2.8)	150 % (1.0–2.5)	–		Sweden	
Coory et al. (14)	1982–2002	45,706		75% (46.9–82.1)	48% (37.4–55.3)	NSC		Thin: 2.8% APC Thick: 2% APC	Thin: 3% APC Thick: NSC	Queensland, Australia	Only data regarding Breslow thickness from 1991–2002
MacKie et al. (15)	1979–2003	4,810	7,640	201% (3.57–10.93)	128% (5.6–12.96)	102% (1.1–2.4)	NSC	< 1 mm: 350% (1.01–4.56) 1–1.99 mm: 334% (0.53–2.30) 2–2.99 mm: 140% (0.43–1.03) 3–3.99 mm: 50% (0.42–0.64) >4 mm: 63% (1.14–1.86)	< 1 mm: 264% (1.81–6.58) 1–1.99 mm: 150% (1.18–2.95) 2–2.99 mm: 20% (0.83–1.0) 3–3.99 mm: –17% (0.59–0.49) >4 mm: 107% (1.17–2.42)	Scotland	No information on statistical significance regarding change in Breslow thickness.
Downing et al. (16)	1993–2003	4,178		46% (5.4–7.9)	75% (7.5–13.1)	No change	–19% (2.7–2.2)	<1.5 mm: 134% (2.6–6.1) 1.5–4 mm: 32% (1.9–2.5) >4 mm: 44% (0.9–1.3)	<1.5 mm: 179% (5.3–9.5) 1.5–4 mm: 73% (1.5–2.6) >4 mm: 80% (0.5–0.9)	Yorkshire, UK	No indication of statistical significance regarding change in mortality or Breslow thickness. Only numbers regarding mortality from 1993 to 2002.
Montella et al. (17)	1984–2006	1,446	2,391	171% (3.1–8.4)	145% (4.9–12.0)	2.6% EAPC	NSC	<1 mm: 390% (1.0–4.9) >4 mm: NSC	<1 mm: 137% (3.0–7.1) NSC amongst other thicknesses	Northern Ireland	No numbers regarding intermediate thicknesses for men.

NSC: no significant change; –: no data available; APC: annual percentage change; EAPC: estimated annual percentage change; TNM: tumour-node-metastasis.
[a]Incidence/100,000/year.

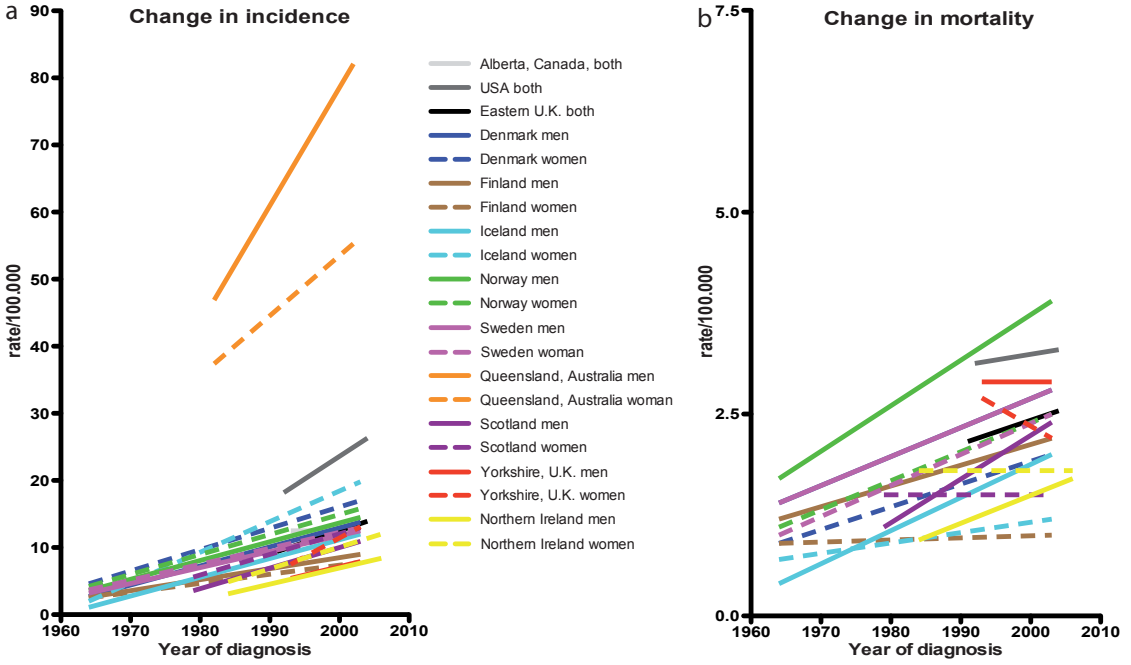

Fig. 1. Change in (a) incidence and (b) mortality. All graphs are a function of 2 or 3 numbers, and should only be used to give an impression of the tendencies.

but a very significant increase compared with earlier incidence rates from 1976. There are unfortunately no data regarding mortality in this study. Montella et al. (17) found the same tendency regarding CMM mortality in women, with a sharp increase in mortality up until just before the study period, and thereafter a slight non-significant decrease. Three more studies found a slight non-significant decrease in mortality; two of them only found a decrease in mortality for women (14, 16). Tryggvadóttir et al. (12) found a slight decrease in mortality for young men, but, most interestingly, they found that most of the increase in mortality was in people over the age of 50 years, and likewise, one found a decrease for both men and women under the age of 65 years, leaving the entire increase in mortality to people over 65 years of age (10).

Breslow thickness and stage

Among the articles, all but one examined Breslow thickness or stage (12, 13). Metelitsa et al. (9) did not describe change in thickness, but only distribution among the different thickness groups, and Levell et al. (11) did not examine changes in Breslow thickness, but according to TNM stage.

All articles except one (10) found a greater increase in thin melanomas than in thick melanomas. Likewise, Levell et al. (11) found a greater increase in TNM stage 1 than in stages 2 and 3, and a decrease in stage 4. Linos et al. (10) found a significant increase in CMM across all different thickness groups, with the highest for very thin melanomas < 1 mm, but interestingly the increase for thick melanomas > 4 mm was nearly as high as for the very thin melanomas. When analysing subgroups this, however, applied only to people over the age of 65 years, for younger people there were no significant changes in either intermediate or thick CMM.

Three more studies reported the incidence change in Breslow thickness among different age groups (15–17), and all three found that most increase in thick melanomas was seen for the oldest group. Montella et al. (9) only found a significant increase in thickness groups, other than for very thin CMM, for men over the age of 50 years. For other groups, there was a significant increase only for very thin melanomas, and a non-significant decrease for thick melanomas (>2.0 mm) in women younger than 50 years.

DISCUSSION

Recent evidence, reviewed here, confirms the previously described trends of a steady increase in incidence of CMM, accompanied by a constant or only a very slight increase in disease-specific mortality. The largest increase in incidence was observed for thin CMM. It has been argued that the increase in melanoma is caused by the overdiagnosis of very early and slow/non-progressing tumours, or even a benign type of melanoma, which have previously escaped the attention of the physicians and patients (3, 5, 11, 18).

Welch & Black (5) argues that two prerequisites must be met for a cancer to be overdiagnosed: (*i*) there must be a disease reservoir, i.e. a pool of very slow-growing or non-progressive cancers, such that patients would die of other causes if they were left untreated;

(*ii*) there must be activities leading to the detection of the disease reservoir, such as screening, increased public awareness, implementation of new diagnostics facilities, etc. In another article Welch et al. (6) have shown that there is a clear correlation between numbers of biopsies taken and numbers of melanomas found; thus the harder one looks, the more melanomas will be found. Theobald et al. (19) have shown that mass media information about skin cancer can lead to an increase in skin self-examination and to an increase in physician consultations and, ultimately, to an increase in CMM incidence. In this study they showed that the incidence of CMM increased by more than 100% the year after a television documentary about CMM, the dangers of sun exposure and the importance of skin self-examination was broadcast. The proportion of very thin CMM also increased by more than 100%.

This, together with the fact that there was no increase in high-stage CMM or mortality, is an indirect indication of the existence of a disease reservoir and prediction that increased public awareness increases the detection rate of early CMM.

The discussion about overdiagnosis in cancer is not restricted to CMM; one of the best examples is the use of prostate-specific antigen (PSA) to screen for prostate cancer. A Cochrane review (20) with a total of 341,351 participants in five studies found no reduction in prostate-specific mortality among test subjects compared with controls. In contrast, there was a 35% increase in diagnosed cancers found compared with the control group. Only one of the studies in the Cochrane review found that screening for prostate cancer decreased mortality. In this study the authors made an intention-to-screen analysis, which showed that a total of 1,410 men need to be screened and 48 new cancers diagnosed in order to prevent one prostate death over a period of 10 years. The authors concluded that PSA screening is unlikely to be beneficial for men with a life expectancy <10–15 years. Since no large-scale randomized trials have been made regarding the effect of screening for CMM (21), similar calculations cannot be conducted for CMM.

A way of estimating the magnitude of a disease reservoir is to estimate the numbers of unidentified cancers in autopsies performed on people who have died of other causes. This has been done for other cancers, such as prostate cancer (22) and thyroid cancer (23), but to our knowledge not for CMM. This could be performed on cohorts of both young and old subjects, in order to evaluate how many, if any, have unidentified CMM at their time of death, and to evaluate possible differences in the cancers in these two groups. If this was done, it might help bring more substantial evidence to the epidemic discussion.

There are other pieces of evidence that make melanoma epidemics unlikely. Approximately 60% of CMM are not discovered by physicians, but by patients themselves or by other non-professionals (24, 25); thus, despite the progress in diagnostic techniques, thicker melanomas should increase in accordance with the overall increase in incidence. Secondly, the progression in treatment of melanomas must follow the increase in incidence closely, or else mortality should increase proportionally to incidence. This implies that the lesions are cured by simple excision at the time of diagnosis (11).

Despite the fact that the existence of a dramatic melanoma epidemic is unlikely, not all new cases of CMM can be dismissed as an overdiagnosis of biologically benign tumours. One study shows a slight increase in thick CMM (10), and in two papers (14, 16) a slight increase in mortality has been observed. It is notable, that increased incidence in thick, advanced CMM is most prominent in the oldest age group (10, 15–17). The same trend appears to occur for mortality (10, 12). It is a well-known phenomenon that the increase in mortality and thick melanomas are highest among elderly people, and cannot be explained entirely by diagnostic delay (26). Elderly patients have the highest proportion of the nodular subtype of CMM, which comprises more than 50% of thick melanomas >2 mm, but only approximately 10% of all CMM. This subtype is characterized by its very rapid growth (21), and is more difficult to diagnose by dermoscopy than the more common superficial spreading CMM (26). Moreover, immune dysfunction in elderly individuals may further contribute to the increase in cancer mortality (26). It is therefore likely that the increase in the incidence of CMM has different consequences depending on age. Lives can probably be saved by more intensive screening of older individuals, whereas intensive screening of young people with no risk factors appears to be obsolete.

The authors declare no conflict of interest.

REFERENCES

1. Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol 2009; 27: 3–9.
2. Dennis LK. Analysis of the melanoma epidemic, both apparent and real. Arch Dermatol 1999; 135: 275–280.
3. Swerlick RA, Chen S. The melanoma epidemic: more apparent than real? Mayo Clin Proc 1997; 72: 559–564.
4. Beddingfield FC 3rd. The melanoma epidemic: res ipsa loquitur. Oncologist 2003; 8: 459–465.
5. Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst 2010; 102: 605–613.
6. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates and incidence of melanoma-population based ecological study. BMJ 2005; 331: 481.
7. Shuster S. Malignant melanoma: how error amplification by screening creates spurious disease. Br J Dermatol 2009; 161: S33–39.
8. Erickson C, Driscoll MS. Melanoma epidemic: facts and controversies. Clin Dermatol 2010; 28: 281–286.
9. Metelitsa AI, Dover DC, Smylie M, de Gara CJ, Lauzon

GJ. A population-based study of cutaneous melanoma in Alberta, Canada (1993–2002). J Am Acad Dermatol 2010; 62: 227–232.
10. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. J Invest Dermatol 2009; 12: 1666–1674.
11. Levell NJ, Beattie CC, Shuster S, Greenberg DC. Melanoma epidemic: a midsummer night's dream? Br J Dermatol 2009; 161: 630–634.
12. Tryggvadóttir L, Gislum M, Hakulinen T, Klint A, Engholm G, Storm HH, et al. Trends in the survival of patients diagnosed with malignant melanoma of the skin in the Nordic countries 1964–2003 followed up to the end of 2006. Acta Oncol 2010; 49: 665–672.
13. Engholm G, Gislum M, Bray F, Hakulinen T. Trends in the survival of patients diagnosed with cancer in the Nordic countries 1964–2003 followed up to the end of 2006. Acta Oncol 2010; 49: 545–560.
14. Coory M, Baade P, Aitken J, Smithers M, McLeod GR, Ring I. Trends for in situ and invasive melanoma in Queensland, Australia, 1982–2002. Cancer Causes Control 2006; 17: 21–27.
15. MacKie RM, Bray C, Vestey J, Doherty V, Evans A, Thomson D, et al. Melanoma incidence and mortality in Scotland 1979–2003. Br J Cancer 2007; 96: 1772–1777.
16. Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993–2003. Br J Cancer 2006; 95: 91–95.
17. Montella A, Gavin A, Middleton R, Autier P, Boniol M. Cutaneous melanoma mortality starting to change: a study of trends in Northern Ireland. Eur J Cancer 2009; 45: 2360–2366.
18. Burton RC, Armstrong BK. Current melanoma epidemic: a nonmetastasizing form of melanoma? World J Surg 1995; 19: 330–333.
19. Theobald T, Marks R, Hill D, Dorevitch A. "Goodbye Sunshine": effects of a television program about melanoma on beliefs, behavior, and melanoma thickness. J Am Acad Dermatol 1991; 25: 717–723.
20. Ilic D, O'Connor D, Green S, Wilt T. Screening for prostate cancer. Cochrane Database Syst Rev 2006; 3: CD004720.
21. Stratigos AJ, Katsambas AD. The value of screening in melanoma. Clin Dermatol 2009; 27: 10–25.
22. Stamatiou K, Alevizos A, Agapitos E, Sofras F. Incidence of impalpable carcinoma of the prostate and of non-malignant and precarcinomatous lesions in Greek male population: an autopsy study. Prostate 2006; 66: 1319–1328.
23. Solares CA, Penalonzo MA, Xu M, Orellana E. Occult papillary thyroid carcinoma in postmortem species: prevalence at autopsy. Am J Otolaryngol 2005; 26: 87–90.
24. Brady MS, Oliveria SA, Christos PJ, Berwick M, Coit DG, Katz J, et al. Patterns of detection in patients with cutaneous melanoma. Cancer 2000; 89: 342–347.
25. Carli P, De Giorgi V, Palli D, Maurichi A, Mulas P, Orlandi C, et al. Self-detected cutaneous melanomas in Italian patients. Clin Exp Dermatol 2004; 29: 593–596.
26. Lasithiotakis KG, Petrakis IE, Garbe C. Cutaneous melanoma in the elderly: epidemiology, prognosis and treatment. Melanoma Res 2010; 20: 163–170.