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Thin or early melanoma, risk factors and associated mortality

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ABSTRACT

INTRODUCTION. The incidence of thin and early-stage melanoma is increasing in many populations, but the clinical significance of these lesions remains partly unknown.

METHODS. Firstly, melanoma deaths in Denmark (2009-2018) were followed back to establish melanoma debut in these persons. Secondly, using national registries of cancer incidence and mortality, 27,036 persons with thin or early-stage melanoma were followed-up for melanoma death.

RESULTS. It is estimated that in 11% of the persons who died from melanoma, the debut was a thin or early-stage melanoma. On follow-up of persons with thin or early-stage melanoma, the 20-year risk of dying from melanoma was 3%.

CONCLUSION. The absolute risk of melanoma death after a diagnosis with thin or early-stage melanoma is low. A subgroup of patients who are at a high risk may possibly be identified by a combination of stage, thickness, ulceration and dermal mitoses.

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A recent Danish study of survival after melanoma of the skin found substantial regional variation in the incidence of stage I and thin melanomas (≤ 1 mm), but no variation in the incidence of more advanced stage and thicker melanomas [1]. Another study reported a marked increase in incidence of all melanoma thicknesses in Denmark from 1985 to 2012, but with a relatively greater increase being recorded for in situ and thin melanomas than thick melanomas [2]. This was also shown in other countries with predominantly fair-skinned populations [3, 4].

Thin melanomas have a much more favourable prognosis than thicker melanomas [5], but from a public health perspective, the death toll of thin melanomas may be significant as they comprise the vast majority of all diagnosed melanomas and are increasing in incidence. A recent Australian study showed that 25% of melanoma deaths debuted with a thin melanoma (≤ 1 mm) [6], indicating the potential severity of thin or early-stage melanomas, as also shown by others [7, 8].

Understanding the variations in incidence and the survival impact of early-stage melanoma is important to

optimise prevention, ensure early diagnosis along with treatment and follow-up of in situ and invasive melanomas [9].

The aim of the present study was to determine the proportion of melanoma deaths in Denmark in the 2009-2018 period in people who originally presented with a thin (≤ 1 mm) or early-stage (in situ or stage I) melanoma. Furthermore, we used the national cohort of melanoma patients to estimate the absolute risk and the tumour-specific risk factors for melanoma death in persons presenting with a thin or early-stage melanoma.

METHODS

Follow-back analysis of melanoma deaths in Denmark

From the Danish Cause of Death Register, we extracted all melanoma deaths, international Classification of Diseases, tenth version (ICD-10) code C43 – melanoma of the skin, for the period from 2009 to 2018. Information on prior melanoma diagnoses was extracted from the Danish Cancer Registry [10] for the period from 1978 to 2018 and from the Danish Melanoma Database (DMD) for 1985-2018 [11]. The DMD contains detailed information on stage and Breslow thickness at the time of diagnosis, including in situ cases and multiple melanomas, and this register was the source of information on stage and melanoma thickness for the analyses. This was so due to lack of these information items back in time for both the Danish Cancer Registry before 2004 and the Danish Pathology Register, which did not gain nationwide coverage until 1997. Stage information in the DMD is registered as separate T, N and M, with the possibility of mapping to different American Joint Committee on Cancer (AJCC) classifications. For this study, we used the AJCC seventh classification as this was used for the main study period (2010-2018).

Linkage with the Danish Cancer Registry was used to exclude melanoma deaths from the analysis when information on stage or thickness was unavailable, either because the patient had been diagnosed before the DMD became operational in 1985 or because the diagnosis record was missing in the DMD but present in the Danish Cancer Registry. For melanoma deaths where diagnosis records were found in both the DMD and the Danish Cancer Registry within ± 90 days, the melanoma database record was used.

We tabulated the covariate distributions for persons who died from melanoma and identified patients who debuted with a thin (≤ 1 mm) or early-stage (in situ or stage I where information about Breslow thickness was not available) melanoma. We identified the persons who had multiple records of melanoma, especially those who had records of thicker or more advanced melanoma in the period between the debuting thin or early-stage melanoma and the melanoma death.

Follow-up analysis of melanoma patients in the Danish Melanoma Database

We used the DMD to identify the national cohort of melanoma patients with a diagnosis of a thin (≤1 mm) or early-stage (in-situ or stage I) melanoma between 1985 and 2018.

Using Kaplan-Meier analysis, we estimated the cause-specific survival function (i.e. with melanoma death as the endpoint) separately for persons who had a thin or early-stage melanoma and persons who had more advanced disease. Furthermore, we performed Cox proportional hazards regression analyses to identify risk factors for melanoma death among those who debuted with a thin or early-stage melanoma.

Trial registration: not relevant.

RESULTS

Follow-back analysis of melanoma deaths in Denmark

A total of 2,735 melanoma deaths were recorded in Denmark in the 2009-2018 period (**Table 1**). We were able to link these records to 1,656 (61%) persons with their first record in the DMD.

TABLE 1 Overview of 2,735 melanoma deaths in Denmark, 2009-2018. The values are n (%).

	Men	Women	Total
Time of death			
2009-2010	289 (18)	221 (19)	510 (19)
2011-2012	347 (22)	220 (19)	567 (21)
2013-2014	331 (21)	273 (24)	604 (22)
2015-2016	321 (20)	212 (18)	533 (19)
2017-2018	290 (18)	231 (20)	521 (19)
1st diagnosis registered in			
The Danish Melanoma Database, 1985-2018[a]	984 (62)	672 (58)	1,656 (61)
The Danish Cancer Register, 1978-2018[a]	411 (26)	308 (27)	719 (26)
Danish Cause of Death Register only, 2009-2018	183 (12)	177 (15)	360 (13)
Subtotal	1,578 (58)	1,157 (42)	2,735 (100)

a) If the dates of 1st diagnosis in the melanoma database and the cancer register were within 90 days, the melanoma database record was used.

Table 2 shows the covariate distributions for the 1,656 melanoma deaths. The proportion with a record of in situ or stage I disease was 16%. The proportion with a record of thin or early-stage melanoma was 12%. A total of 26% had a missing stage value and 17% had a missing value for thickness, but all records had one or the other covariate. We therefore combined thickness and stage information into a risk group and identified 205 patients in the "thin or early stage" risk group as those who had either a thickness ≤ 1 mm or stage in situ or I.

TABLE 2 Overview of 1,656 melanoma deaths with a first diagnosis of melanoma registered in the Danish Melanoma Database.

	n (%)
Morphology	
Lentigo maligna melanoma	44 (3)
Nodular melanoma	354 (21)
Superficial spreading melanoma	821 (50)
Other and NA	437 (26)
Tumour stage[a]	
In situ	20 (1)
IA	100 (6)
IB	146 (9)
IIA	148 (9)
IIB	153 (9)
IIC	118 (7)
III	439 (27)
IV	109 (7)
NA	423 (26)
Breslow thickness	
≤ 1 mm	180 (11)
> 1-2 mm	321 (19)
> 2 mm	868 (52)
NA	287 (17)
Risk group	
Thin or early stage[b]	205 (12)
Thick or advanced stage[c]	1,451 (88)
Ulceration? (p = 0.81)	
Yes	647 (39)
No	843 (51)
NA	166 (10)

NA = not available.
a) American Joint Committee on Cancer, 7th ed.
b) Either ≤ 1 mm or stage in situ or I, some have missing value for thickness or stage but 0 has thickness > 1 mm or ≥ stage II.
c) All records with either > 1 mm or ≥ stage II.

In the time interval between debut with thin or early-stage melanoma and melanoma death, 20 of the 205 persons had further records in the DMD with a more advanced melanoma. This left 185 patients with thin or early-stage melanoma and no record of advanced disease.

We thus found that 11% (185 cases) of the Danish melanoma deaths occurred in a person diagnosed with a thin or early-stage melanoma and with no record of more advanced disease.

Follow-up analysis of melanoma patients in the Danish Melanoma Database

According to the DMD, a total of 46,264 melanoma patients were diagnosed in Denmark in the 1985-2018 period.

Using the same criteria for classification into risk groups as in Table 2, a total of 27,036 (58%) were thin or early stage and 19,228 (42%) were of a more advanced stage at their diagnosis.

Figure 1 shows the Kaplan-Meier analysis of cause-specific mortality for the two groups. At 20-year follow-up, the cumulative risk of melanoma death was 3% (95% confidence interval (CI): 2-3%) in patients with thin or early-stage melanoma and 17% (95% CI: 16-18%) in patients with more advanced melanoma.

FIGURE 1 Kaplan Meier cause-specific survival functions for 46,264 patients with thin or early-stage melanoma (n = 27,036) and thick or advanced stage melanoma (n = 19,228).

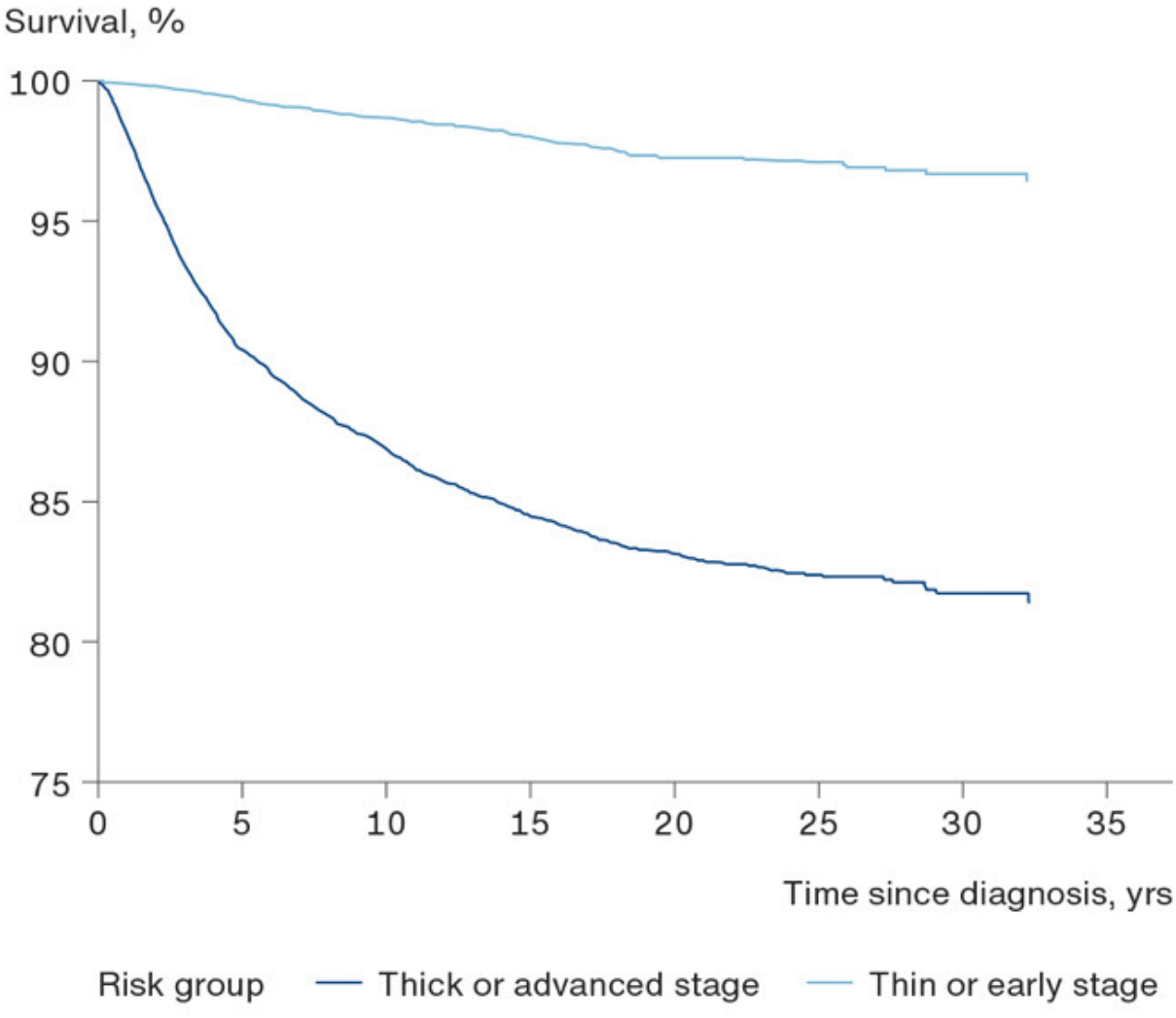

Table 3 shows the Cox regression analysis of risk factors for melanoma death in patients debuting with thin or early-stage melanoma, with each estimate adjusted for year of diagnosis, age and sex. The analysis identified a higher mortality for invasive melanoma (compared with in-situ lesions), melanoma with a thickness of 0.8-1 mm, melanomas of the nodular subtype and melanoma with ulceration or presence of mitoses in the dermal melanoma cells.

TABLE 3 Cox regression analysis of cause-specific mortality in 27,036 patients debuting with thin or early-stage melanoma.

		Adjusted HR[a]	
	n (%)	HR (95% CI)	p-value[b]
Stage[c]			< 0.0001
In situ	6,794 (25)	0.34 (0.22-0.53)	
Stage I	14,955 (55)	1.00 (ref.)	
NA	5,287 (20)	1.08 (0.78-1.47)	
Breslow thickness			< 0.0001
≤ 0.8 mm	16,080 (59)	1.00 (ref.)	
> 0.8-1 mm	3,291 (12)	2.59 (2.01-3.33)	
NA	7,665 (28)	0.76 (0.54-1.07)	
Morphology			< 0.0001
Lentigo maligna melanoma	2,437 (9)	0.73 (0.45-1.20)	
Nodular melanoma	240 (1)	5.36 (3.12-9.20)	
Superficial, spreading melanoma	22,948 (85)	1.00 (ref.)	
Other and NA	1,411 (5)	2.02 (1.40-2.91)	
Ulceration?			< 0.0001
Yes	424 (2)	3.30 (1.99-5.48)	
No	25,364 (94)	1.00 (ref.)	
NA	1,248 (5)	1.28 (0.84-1.95)	
Mitotic index			0.01
0	7,663 (28)	1.00 (ref.)	
≥ 1	1,857 (7)	3.43 (1.88-6.27)	
NA	17,516 (65)	1.32 (0.80-2.20)	

CI = confidence interval; HR = hazard ratio; NA = not available; ref. = reference.
a) Adjusted for age, year of diagnosis and sex.
b) Tests for heterogeneity in the five simpler regression models.
c) American Joint Committee on Cancer, 7th ed.

DISCUSSION

Recapitulation of main results

We did a follow-back analysis of Danish melanoma deaths (2009-2018) and a follow-up analysis of thin and early-stage melanoma diagnosed in the 1985-2018 period. Patients with thin or early-stage melanoma contributed about 11% of the total burden of melanoma deaths. The absolute risk of melanoma death in the 20-year period after diagnosis with thin or early-stage melanoma was 3%. Prognostic factors for melanoma death in these patients are variables that are usually known for melanoma: stage I versus in situ, thickness, ulceration and dermal mitoses.

Limitations of the data

Data on melanoma thickness and stage are not routinely available in the Danish Cancer Registry but have been included in the DMD as from 1985. Linkage between these two datasets indicated that case ascertainment in the DMD was less than complete. Some records were registered in the Danish Cancer Registry before the melanoma database became operational. However, the loss of study population (Table 1) was mostly due to incomplete case registration in the melanoma database, mainly in the first years after the database became operational. Data in the DMD are contributed by specialist departments of pathology and plastic surgery or, to a lesser extent, dermatology or oncology. The triggering event is typically the surgical removal of a skin lesion or the clinical follow-up of a pathology verified melanoma removed in general practice, by a private practising dermatologist or a plastic surgeon. We consider it most likely that the under-registration is independent of tumour characteristics but due mainly to the contribution of data to the database from individual hospital departments. In any case, the analyses are based on incomplete (though unselected) data, and the results should therefore be interpreted with caution.

At different time periods, the priority has been to record the extent and severity of disease as Breslow thickness or as TNM stage, and many records had only one of these variables recorded. We have therefore chosen to combine the variables in the definition of "thin or early stage" melanoma. We considered this necessary to retain the integrity of the dataset and justified because thickness is part of the definition of the TNM stage. Results in Table 3 verify that both thickness and stage are strong predictors of survival, even within thin or early-stage lesions.

The follow-back analysis included 20 patients with in situ melanomas and melanoma death. An explanation for this may be changes in tumour classification over time, since the tumours were diagnosed from 1985 to 2018. The first four AJCC classifications (from 1977 to 1997) included Breslow thickness as a parameter but held no information on how to report thickness in case of regression. A remaining in situ component in a melanoma with regression of the dermal component may thus have been reported or registered as an in situ melanoma, a diagnosis which in this case does not reflect the metastatic potential of the tumour. Another explanation may be that a small invasive focus was not included in the analysed sections.

The progression of early melanoma

Even though registration of relapse in the DMD is mandatory, it is underreported and especially so for the early period of the data collection. Therefore, we lack information on progression and treatment in the period from thin or early stage to death that may potentially provide information about, e.g., the timing of and the nature of the first recurrence. If a thin melanoma becomes fatal, it generally does so later than in thicker melanomas. This is a well-known clinical experience and was also reflected in this dataset. The reason for this remains unknown but is possibly influenced by multiple factors including tumour biology, i.e. tumour cell characteristics, the microenvironment in the tumour-bed, the tumour cells' capacity for dissemination and the patient's immune response and capability of destroying tumour cells [12]. When a tumour reappears several years after the initial treatment, it is believed that metastatic cells have been dormant locally in the lymph nodes or in distant tissues, and due to some unknown influence suddenly become activated and then divide, mutate and grow. Melanoma may re-appear after a free interval because untreated micro-foci left behind after the initial surgery, and metastatic lesions may appear decades after the initial treatment [12].

Once a recurrence appears, the primary tumour characteristics no longer have the same prognostic importance; the metastatic lesion "overrules" the original parameters. Still, not all metastases are the same; they are dependent on the number and character of mutations, the growth rate, etc., as well as on predilection sites [13]. It is also well known that tumour clones differ over time, drug resistance develops and the most aggressive and rapidly growing clones will eventually become dominant.

Clinical implications

It is reassuring that we found only 3% melanoma-specific mortality within 20 years for Danish patients with thin or early-stage melanomas. This concurs with findings reported from a recent large Swedish study; among 31,670 patients with thin melanomas, overall ten- and 20-year melanoma-specific survival rates of 97% (95% CI: 97-97%) and 95% (95% CI: 95-96%) , respectively were found [14]. In an Australian study of 2,117 T1 cases treated at a specialised referral centre, ten- and 20-year melanoma-specific survival rates for those with tumours up to 0.8 mm thick were 93.4 and 85.7%, respectively; and for tumours 0.9 to 1.0 mm, the rates were 81.1% and 71.4%, respectively [15]. These survival rates are much poorer than the Danish and Swedish figures, but differences in database information, case mix and population characteristics may account, in part, for this.

The combined evidence is that thin melanoma may ultimately be fatal, and there are identifiable risk factors for these deaths: stage, thickness, ulceration and dermal mitoses. These risk factors give a basis for risk stratification and are in accordance with other studies [5, 14]. Thickness and ulceration are parameters included in the AJCC/Union for International Cancer Control (UICC) classification of cutaneous melanoma as a cut-off for subdivision of T1a and T1b [16]. Sentinel node biopsy in patients with thin melanoma with risk factors such as ulceration and mitosis may be beneficial to accurate staging [17] and may improve survival [18]. In contrast, the new 2022 national guidelines for sentinel node biopsy for T1 tumours only recommend sentinel node biopsy in the presence of mitoses, as this has been found to be a stronger predictor for micro-metastases than ulceration [17, 19], and a positive sentinel node may indicate adjuvant therapy. Tools allowing us to predict outcomes even in patients with thin melanoma have been developed and may help to identify patients with thin melanoma who are at a high risk of recurrence [18, 20].

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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