


The relative contribution of the decreasing trend in tumour thickness to the 2010s increase in net survival from cutaneous malignant melanoma in Italy: a population-based investigation*

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Linked Comment: I.T. Harvima and R.J. Harvima. *Br J Dermatol* 2022; **187**:6–7.

Abstract

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Accepted for publication

6 February 2022

Funding sources

This work was supported by the Italian Melanoma Intergroup and the Italian Ministry of Health.

Conflicts of interest

The authors declare they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the Italian Association of Cancer Registries (AIRTUM). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the corresponding author with the permission of the Italian Association of Cancer Registries (AIRTUM).

Details of the AIRTUM Working Group can be found in Appendix 1.

A full list of affiliations can be found in Appendix 2.

This study was presented at the International Association of Cancer Registries virtual annual conference, 12–14 October 2021, and received the Elvo

Background The long-term increase in survival from cutaneous malignant melanoma (CMM) is generally attributed to the decreasing trend in tumour thickness, the single most important prognostic factor.

Objectives To determine the relative contribution of decreased tumour thickness to the favourable trend in survival from CMM in Italy.

Methods Eleven local cancer registries covering a population of 8 056 608 (13.4% of the Italian population in 2010) provided records for people with primary CMM registered between 2003 and 2017. Age-standardized 5-year net survival was calculated. Multivariate analysis of 5-year net survival was undertaken by calculating the relative excess risk (RER) of death. The relative contribution of the decrease in tumour thickness to the RER of death was evaluated using a forward stepwise flexible parametric survival model including the available prognostic factors.

Results Over the study period, tumour thickness was inversely associated with 5-year net survival and multivariate RER in both sexes. The median thickness was 0.90 mm in 2003–2007, 0.85 mm in 2008–2012 and 0.75 mm in 2013–2017 among male patients, and 0.78 mm, 0.77 mm and 0.68 mm among female patients, respectively. The 5-year net survival was 86.8%, 89.2% and 93.2% in male patients, and 91.4%, 92.0% and 93.4% in female patients, respectively. In 2013–2017, male patients exhibited the same survival as female patients despite having thicker lesions. For them, the increasing survival trend was more pronounced with increasing thickness, and the inclusion of thickness in the forward stepwise model made the RER in 2013–2017 vs. 2003–2007 increase from 0.64 [95% confidence interval (CI) 0.51–0.80] to 0.70 (95% CI 0.57–0.86). This indicates that the thickness trend accounted for less than 20% of the survival increase. For female patients, the results were not significant but, with multiple imputation of missing thickness values, the RER rose from 0.74 (95% CI 0.58–0.93) to 0.82 (95% CI 0.66–1.02) in 2013–2017.

Tempia Special Prize. The article is based on a thesis submitted to the School of Medicine at the University of Pavia, Pavia, Italy, as part of F.Z.'s Level II Professional Master's Programme in Biostatistics and Epidemiological Methodology.

*Plain language summary available online

DOI 10.1111/bjd.21051

Conclusions For male patients in particular, decrease in tumour thickness accounted for a small part of the improvement in survival observed in 2013–2017. The introduction of targeted therapies and immune checkpoint inhibitors in 2013 is most likely to account for the remaining improvement.

What is already known about this topic?

- Long-term increase in survival from cutaneous malignant melanoma (CMM) is generally attributed to the decreasing trend in tumour thickness, the single most important prognostic factor.
- Targeted therapies and immune checkpoint inhibitors, introduced during the past decade, were shown in phase III trials to improve the prognosis of patients with unresectable and metastatic CMM, but their contribution to the persistent upward trend in overall survival at the population level in Europe is ill-defined.

What does this study add?

- In Italy, the 5-year net survival from CMM in 2013–2017 improved vs. 2003–2007, especially among male patients and in the two highest tumour thickness categories.
- Male patients, for the first time, exhibited the same survival as female patients despite having still thicker lesions. The decrease in median tumour thickness accounted for a small part of the improvement.
- Novel therapies, approved in 2013, are the factor most likely to account for the remaining improvement.

Since approximately the end of World War II, the incidence of cutaneous malignant melanoma (CMM) has steeply increased in white populations all over the world.^{1–8} This has been the result of a critical change in sunbathing habits with more intermittent and intense ultraviolet radiation exposure^{9–10} coupled with an increased use of artificial ultraviolet radiation-emitting indoor tanning beds.

The incidence increase has been primarily driven by patients with early cases of CMM, defined as having a low Breslow tumour thickness. The incidence of thick CMM has also increased, but to a lesser extent.^{11–15} This pattern is compatible with the following three explanations, which are not mutually exclusive: increased public awareness of the signs of the disease, resulting in earlier detection; decreased biological aggressiveness of sun-related CMM, which would be suggested by the positive association between the level of ultraviolet radiation exposure before diagnosis and survival from the disease;^{16,17} and increased sensitivity of dermatological screening for early CMM,¹⁸ possibly associated with a risk of overdiagnosis.^{18,19}

Whatever its cause, the tumour-thickness-specific incidence trends have been generally paralleled by an increase in survival.^{20,21} As a low tumour thickness is the single major prognostic factor for the outcome of patients with CMM,²² the most important epidemiological studies have related the upward survival trend to the rise in incidence of thin lesions.^{23,24}

This temporal correlation, however, is not necessarily evidence for a causal and exclusive link. According to studies from Germany²⁵ and Australia,²⁶ the increase in survival

occurring in the last two decades of the last century was only partially attributable to early detection.²⁵ More recent data from the USA have shown a survival improvement in all tumour stage categories,¹³ including thick and metastatic disease and, thus, independently of changes in tumour thickness.²⁷ This is interpreted as the result of the introduction of molecular targeted therapies and immune checkpoint inhibitors during the past decade.²⁸

In view of their potential implications on policies for secondary prevention and treatment of CMM on a public health scale, these important observations need to be confirmed in other populations. We report a multicentre cancer registry-based study exploring in a formal fashion the relationship between the trend in tumour-thickness-specific incidence and the trend in survival from CMM in Italy.

Materials and methods

Rationale and objectives

Over the past three decades, the incidence of CMM in Italy has constantly increased.²⁹ Several local studies have already suggested that this trend has been more pronounced for thin CMM.^{30,31} As found elsewhere, the reduction in tumour thickness has been accompanied by a consistent increase in 5-year survival rates.³²

The present study was designed to gain a better understanding of the relationship between these parallel trends. The

primary objective was to quantify the relative role that the lowering of tumour thickness has played in the favourable survival trend in the Italian adult population (age ≥ 15 years). In order to corroborate the study rationale, we identified all significant prognostic factors among the available registration variables, we assessed their time trends, and we studied in detail the trend in survival.

The study protocol was approved by the Ethics Committee at the Romagna Cancer Institute (ID: IRST100.37; IRST identifier codes: L1P1572, wfn.75L1).

Source of data

The data for the study were extracted from the database of the Italian Association of Cancer Registries (AIRTUM) using the International Statistical Classification of Diseases and Related Health Problems, 10th revision, codes C43.0 to C43.9.³³ Although not included in the standard registration items³⁴ nor reported in routine statistical publications,³⁵ tumour thickness has been regularly recorded for many years by several Italian registries.

Sixteen cancer registries with available tumour thickness information authorized the use of their records. Their data, pooled together, covered the years 1989–2017. The analysis was restricted to the registries that have been operating for ≥ 10 consecutive years with an annual proportion of cases with missing tumour thickness information $\leq 25\%$. Eleven registries, with a core registration period of 15 years, met these criteria. On 1 January 2010, they covered a total population of 8 056 608 (13.4% of the Italian population). The population aged ≥ 15 years was 6 904 734.

Case series

The participating registries contributed a total of 17 707 cases of CMM to the study. Among these there were 26 death-certificate-only (DCO) cases (a proportion of 0.15%, a measure of incompleteness of cancer registration). DCO cases as well as cases registered based on an autopsy report and those with no follow-up data ($n = 33$) were excluded leaving 17 674 cases eligible for analysis. Table S1 (see Supporting Information) shows details of each participating registry.

The 17 674 eligible CMM cases were from 9108 male patients (51.5%) and 8566 female patients (48.5%). The number that could be categorized by tumour thickness according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging criteria³⁶ was 8246 and 7884, respectively, with a total of 16 130 (91.3%).

Tumour thickness categorization

In accordance with the above mentioned AJCC staging criteria,³⁶ tumour thickness was categorized as < 0.8 , 0.8 – 1.0 , > 1.0 – 2.0 , > 2.0 – 4.0 and > 4.0 mm. In general, thin CMM is defined as having a thickness ≤ 1.0 mm.^{11,14,15,37} In accordance with the International Classification of Diseases for

Oncology – 3rd edition, 1st revision,²⁴ histological subtype was categorized as superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, or other.

Statistical methods

We estimated 5-year net survival using the Pohar–Perme estimator.³⁸ The estimates of 5-year net survival, obtained with the *strs* Stata command and based on a traditional cohort (or complete) approach,³⁹ were age-standardized with the International Cancer Survival Standard-2 weights.⁴⁰ Patients were followed-up until 31 December 2018. To correct for the background mortality, we constructed registry-specific life tables.

To assess the trends in the incidence of CMM according to their prognostic features, the average annual per cent change was estimated (EAAPC). For this purpose, a generalized linear regression model for the natural logarithm of the age-standardized incidence rates, with calendar year as a regressor variable, was fitted.

To assess the statistical significance of the trend in 5-year net survival, a Poisson regression model for net survival including the period of diagnosis as a continuous regressor was used. Specifically, the statistical significance was assessed with the Wald test for trend [P-value and the 95% confidence interval (CI)] in the exponential of the period of diagnosis coefficient.

Multivariate analysis of 5-year net survival was undertaken by calculating the relative excess risk (RER) of death.⁴¹ A flexible parametric survival model using restricted cubic splines (five degrees of freedom for male patients and six for female patients) was fitted on the log cumulative excess hazard scale.⁴² Flexible parametric models for net survival were fitted on individual-level data by using the *stpm2* Stata command.⁴³

The study period was divided into time periods of equal length. In order to increase the robustness of results, three 5-year periods (2003–2007, 2008–2012, 2013–2017) were preferred to five 3-year periods. To determine the relative contribution of the decrease in tumour thickness to survival improvement, the years 2003–2007 were used as a reference period. A forward stepwise selection method was used to add variables to the model, with the statistical significance of each predictor being determined by the log-likelihood ratio test for nested models with a P-value less than 0.05.

To deal with the problem of participants with CMM where there was missing tumour thickness information, a sensitivity analysis of the multivariate RER of death by time period of diagnosis was performed. Two different methods were used: classifying tumour thickness according to the five AJCC categories plus a category for missing values and performing the multiple imputation of missing values under the ‘missing at random’ assumption.⁴⁴ Ten imputations were performed. The variables used included patient age, sex, time period of diagnosis, basis of diagnosis, vital status, histological subtype, tumour subsite and follow-up time. The statistical significance of age at diagnosis, histological subtype and tumour subsite was determined with the log-likelihood ratio test for nested models. For tumour thickness, the Wald test was used.⁴⁵

Further details are provided in the footnotes to Table S2 (male patients) and Table S3 (female patients) in the Supporting Information.

The cases of the 16 130 patients that could be classified into the five AJCC tumour thickness categories formed the basis for the identification of prognostic factors, the evaluation of time trend in incidence by prognostic characteristics, the evaluation of time trend in 5-year net survival and the stepwise multivariate analysis of survival. The total series of cases from 17 674 patients was used for the sensitivity analysis.

All statistical analyses were performed by using the Stata statistical package, Release 15.1 (StataCorp, College Station, TX, USA).

Results

Among the cases from the 16 130 patients with available tumour thickness information, the median patient age was 62 years for the 8246 male patients and 55 years for the 7884 female patients. Nearly half of these were diagnosed with a CMM ≤ 0.8 mm thick (male patients, 46.2%; female patients, 52.0%), and a comparable proportion presented with a superficial spreading melanoma (male patients, 45.9%; female patients, 49.3%).

Prognostic factors

Significant prognostic factors for 5-year net survival were identified for the study period as a whole. Table 1 shows the association of patient age and disease characteristics with 5-year net survival by sex. The strong inverse prognostic value of tumour thickness was confirmed both for male and female patients. Five-year net survival decreased markedly with increasing patient age. There also was significant heterogeneity in survival between histological subtypes and, for male patients, between tumour subsites. Over the whole study period, female patients survived longer than male patients, with a 5-year net survival of 92.2% (95% CI 91.3–93.1%) vs. 89.7% (95% CI 88.7–90.7%) (Wald test, $P < 0.001$) (data not shown).

As shown in Table 2, multivariate analysis of 5-year net survival based on the calculation of the RER of death, confirmed the prognostic significance of tumour thickness and patient age for both sexes. The survival gradient across tumour thickness categories was particularly pronounced.

Time trend in incidence by prognostic characteristics

Table 3 shows that the age-standardized incidence rate increased significantly over time for many prognostic

Table 1 Number of patients with cutaneous malignant melanoma and 5-year per cent net survival by patient age, tumour thickness, histological subtype and tumour subsite, by sex, Italy, 2003–2017

	Male patients			Female patients		
	n (%)	% net survival (95% CI)	P-value	n (%)	% net survival (95% CI)	P-value
Age at diagnosis, years ^a			< 0.001			< 0.001
15–44	1597 (19.4)	93.5 (92.2–94.8)		2372 (30.1)	96.7 (95.9–97.5)	
45–64	2973 (36.1)	91.4 (90.1–92.7)		2735 (34.7)	95.0 (94.0–96.0)	
≥ 65	3676 (44.6)	83.9 (81.4–86.5)		2777 (35.2)	83.9 (81.2–86.8)	
Thickness (mm)			< 0.001			< 0.001
< 0.8	3812 (46.2)	102.2 (101.1–103.3)		4096 (52.0)	102.5 (101.5–103.5)	
0.8–1.0	853 (10.3)	99.9 (97.3–102.5)		915 (11.6)	100.3 (98.0–102.7)	
> 1.0–2.0	1345 (16.3)	91.7 (89.3–94.2)		1240 (15.7)	93.1 (90.8–95.5)	
> 2.0–4.0	1197 (14.5)	72.7 (69.5–76.1)		873 (11.1)	77.2 (73.8–80.8)	
> 4.0	1039 (12.6)	51.7 (47.5–56.3)		760 (9.6)	54.1 (49.0–59.9)	
Histological subtype			< 0.001			< 0.001
SSM	3782 (45.9)	96.2 (94.9–97.6)		3887 (49.3)	96.9 (95.7–98.2)	
NM	1114 (13.5)	68.5 (65.0–72.3)		845 (10.7)	73.3 (69.8–77.1)	
LMM	283 (3.4)	100.7 (97.6–103.8)		317 (4.0)	101.4 (98.9–103.9)	
Other subtypes	2358 (28.6)	87.0 (85.1–88.9)		2232 (28.3)	90.9 (89.2–92.7)	
Melanoma NOS	709 (8.6)	94.2 (91.2–97.4)		603 (7.6)	93.4 (90.2–96.8)	
Tumour subsite			< 0.001			0.293
Head and neck	1157 (14.0)	84.1 (80.9–87.4)		870 (11.0)	90.2 (87.3–93.2)	
Trunk	4142 (50.2)	90.5 (89.1–91.9)		2310 (29.3)	92.1 (90.2–94.0)	
Upper limb	1516 (18.4)	91.2 (88.9–93.6)		1446 (18.3)	93.7 (91.7–95.6)	
Lower limb	1173 (14.2)	88.0 (85.3–90.6)		2951 (37.4)	92.3 (90.9–93.7)	
Other	258 (3.1)	89.3 (83.9–95.0)		307 (3.9)	88.7 (83.5–94.2)	

CI, confidence interval; LMM, lentigo maligna melanoma; NM, nodular melanoma; NOS, not otherwise specified; SSM, superficial spreading melanoma. ^aFor age at diagnosis, the age-specific 5-year per cent net survival is shown. For the remaining variables, 5-year net survival was age-standardized using the International Cancer Survival Standard-2 weights.⁴⁰ P-values, from a Wald test for survival comparison, refer to the variable's coefficient estimated by fitting a generalized linear model for net survival, with Poisson distribution, including the follow-up time, the age at diagnosis and the covariate.

Table 2 Multivariate relative excess risk (RER) of death from cutaneous malignant melanoma by patient age, tumour thickness, histological subtype and tumour subsite, by sex, Italy, 2003–2017^a

	Male patients			Female patients		
	Deaths, n (%)	RER (95% CI)	P-value	Deaths, n (%)	RER (95% CI)	P-value
Age at diagnosis, years			< 0.001			< 0.001
15–44	99 (6.2)	1.00 (ref)		74 (3.1)	1.00 (ref)	
45–64	301 (10.1)	1.08 (0.84–1.39)		156 (5.7)	1.15 (0.84–1.57)	
≥ 65	1153 (31.4)	1.47 (1.16–1.87)		769 (27.7)	1.88 (1.40–2.52)	
Thickness (mm)			< 0.001			< 0.001
< 0.8	239 (6.3)	0.00 (0.00–)		115 (2.8)	0.00 (0.00–)	
0.8–1.0	79 (9.3)	0.11 (0.03–0.50)		36 (3.9)	0.00 (0.00–)	
> 1.0–2.0	219 (16.3)	1.00 (ref)		148 (11.9)	1.00 (ref)	
> 2.0–4.0	435 (36.3)	3.75 (2.81–4.99)		269 (30.8)	3.27 (2.36–4.53)	
> 4.0	581 (55.9)	8.20 (6.17–10.89)		431 (56.7)	8.59 (6.22–11.88)	
Histological subtype			0.643			0.530
SSM	414 (10.9)	1.00 (ref)		260 (6.7)	1.00 (ref)	
NM	466 (41.8)	0.91 (0.73–1.14)		326 (38.6)	0.92 (0.71–1.19)	
LMM	54 (19.1)	0.26 (0.03–2.15)		47 (14.8)	0.49 (0.18–1.37)	
Other subtypes	519 (22.0)	0.94 (0.75–1.17)		304 (13.6)	0.85 (0.66–1.11)	
Melanoma NOS	100 (14.1)	0.84 (0.59–1.21)		62 (10.3)	0.81 (0.52–1.28)	
Tumour subsite			0.211			0.094
Head and neck	343 (29.6)	1.00 (ref)		225 (25.9)	1.00 (ref)	
Trunk	670 (16.2)	0.88 (0.71–1.09)		191 (8.3)	1.08 (0.79–1.48)	
Upper limb	280 (18.5)	0.79 (0.61–1.02)		168 (11.6)	0.81 (0.58–1.13)	
Lower limb	211 (18.0)	0.74 (0.57–0.97)		364 (12.3)	0.80 (0.60–1.07)	
Other	49 (19.0)	0.89 (0.55–1.44)		51 (16.6)	1.08 (0.68–1.73)	

CI, confidence interval; LMM, lentigo maligna melanoma; NM, nodular melanoma; NOS, not otherwise specified; ref, reference; SSM, superficial spreading melanoma. ^aThe RER of death is from a flexible parametric model for net survival with 5 degrees of freedom for male patients and 6 degrees of freedom for female patients. The number of degrees of freedom corresponds to the number of the model with the lowest Akaike information criterion. The numbers of deaths and the RER of death were calculated for 5 years since diagnosis. Estimates were performed adjusting for all the variables in the table and for the time period of diagnosis. P-values are for the Wald test.

categories of CMM, but with different increments. In particular, the EAAPC was greater for patients aged ≥ 45 years as well as for superficial spreading melanoma compared with the nodular subtype. The incidence increase was particularly remarkable among CMMs < 0.8 mm thick, the largest tumour thickness category. The EAAPC was less and less pronounced in the three intermediate categories, but rising again for the small subgroup of cases > 4.0 mm thick.

As illustrated in Figure 1, these different tumour-thickness-specific incidence trends led to an overall decrease in the median tumour thickness of incident CMM cases, which was steeper among cases in male patients. In 2013–2017, however, male patients still had a disadvantage in terms of tumour thickness distribution, even though the difference from that in female patients narrowed.

Time trend in 5-year net survival

Also shown in Figure 1, the time period of diagnosis was positively associated with 5-year net survival. Three important aspects should be noted.

First, the increase in survival was not significant for female patients, because of their high baseline net survival, but the exponential of the period of diagnosis coefficient

was 0.89, with a 95% CI 0.77–1.03, slightly over 1. Male patients experienced a more marked and significant improvement. Thanks to this, and despite the fact they were still diagnosed with lesions of higher median tumour thickness, male patients virtually reached, in 2013–2017, the same 5-year net survival as female patients (93.2% vs. 93.4%).

Second, as shown in Figure 2, the improvement in 5-year net survival for male patients was more pronounced, both in absolute and relative terms, in the tumour thickness categories > 2.0–4.0 mm and > 4.0 mm. Regarding male patients, it is also worthy of note that for the most part the increase in survival occurred from 2013 onwards.

And third, this increase in survival occurred despite the fact that, among male patients, the median tumour thickness in the category of CMMs > 4.0 mm thick rose from 6.21 mm in 2008–2012 to 6.90 mm in 2013–2017 (data not shown).

Stepwise multivariate analysis of survival

The role of the decrease in tumour thickness in determining the improvement in survival is illustrated in Table 4. Female patients were retained in the analysis considering the P-value and the 95% CI of the exponential of the period of diagnosis

Table 3 Average annual cutaneous malignant melanoma incidence rates per 100 000 persons and estimated average annual per cent change by patient age, tumour thickness, histological subtype and tumour subsite, by sex, Italy, 2003–2017^a

	Male patients		Female patients	
	ASIR (95% CI)	EAAPC (95% CI)	ASIR (95% CI)	EAAPC (95% CI)
Age at diagnosis, years				
15–44	7.3 (6.9 to 7.7)	3.4* (2.2 to 4.6)	10.9 (10.5 to 11.4)	2.5* (1.0 to 4.0)
45–64	21.6 (20.8 to 22.4)	5.0* (4.3 to 5.6)	18.8 (18.1 to 19.5)	4.7* (3.7 to 5.7)
≥ 65	39.1 (37.9 to 40.4)	5.7* (4.7 to 6.7)	21.8 (21.0 to 22.6)	4.1* (3.2 to 4.9)
Thickness, mm				
< 0.8	8.8 (8.5 to 9.0)	7.3* (6.0 to 8.5)	8.4 (8.2 to 8.7)	5.1* (3.7 to 6.5)
0.8–1.0	2.0 (1.8 to 2.1)	4.5* (2.8 to 6.2)	1.9 (1.8 to 2.0)	3.0* (0.7 to 5.3)
> 1.0–2.0	3.1 (3.0 to 3.3)	2.6* (1.4 to 3.9)	2.5 (2.4 to 2.7)	1.2* (0.3 to 2.2)
> 2.0–4.0	2.8 (2.7 to 3.0)	2.3* (0.8 to 3.8)	1.7 (1.6 to 1.8)	1.5* (0.1 to 3.0)
> 4.0	2.5 (2.4 to 2.7)	3.7* (2.5 to 5.0)	1.4 (1.3 to 1.5)	3.8* (2.3 to 5.4)
Histological subtype				
SSM	8.7 (8.4 to 9.0)	3.5* (2.3 to 4.8)	8.0 (7.8 to 8.3)	2.3* (1.1 to 3.6)
NM	2.7 (2.5 to 2.8)	0.0 (–2.1 to 2.1)	1.6 (1.5 to 1.7)	–0.7 (–3.4 to 1.9)
LMM	0.7 (0.6 to 0.8)	1.5 (–2.9 to 5.8)	0.6 (0.5 to 0.6)	2.1 (–1.7 to 5.9)
Other subtypes	5.5 (5.3 to 5.8)	9.0* (7.2 to 10.9)	4.5 (4.3 to 4.7)	8.1* (5.5 to 10.6)
Melanoma NOS	1.6 (1.5 to 1.8)	7.1* (5.1 to 9.1)	1.2 (1.1 to 1.3)	4.9* (2.6 to 7.2)
Tumour subsite				
Head and neck	2.8 (2.6 to 3.0)	3.5* (2.1 to 5.0)	1.6 (1.5 to 1.7)	0.3 (–1.5 to 2.1)
Trunk	9.6 (9.3 to 9.9)	6.0* (4.8 to 7.1)	4.8 (4.6 to 5.0)	5.6* (4.4 to 6.9)
Upper limb	3.5 (3.4 to 3.7)	4.6* (3.1 to 6.0)	2.9 (2.8 to 3.1)	3.4* (1.8 to 4.9)
Lower limb	2.7 (2.5 to 2.9)	3.7* (2.1 to 5.4)	6.0 (5.8 to 6.2)	3.1* (2.0 to 4.2)
Other	0.6 (0.5 to 0.7)	7.9* (2.6 to 13.3)	0.6 (0.5 to 0.7)	8.6* (3.3 to 14.0)

ASIR, age-standardized incidence rate; CI, confidence interval; EAAPC, estimated average annual per cent change; LMM, lentigo maligna melanoma; NM, nodular melanoma; NOS, not otherwise specified; SSM, superficial spreading melanoma. ^aEstimated average annual per cent change is from a generalized linear model for the natural logarithm of the age-standardized incidence rates with calendar year as a regressor variable. *Significantly different from zero at the alpha level of 0.05.

coefficient (0.77–1.03) (Figure 1). The years 2003–2007 were used as a reference period.

In 2008–2012, male patients had a RER of death nonsignificantly lower than the unity at all steps of the model, although the RER increased from 0.82 to 0.91 when tumour thickness was entered. For the years 2013–2017, the baseline model including the period of diagnosis alone yielded an unadjusted RER of death as low as 0.63. With the simultaneous inclusion of patient age, histological subtype and tumour subsite as explanatory factors, the RER of death was virtually unchanged at 0.64. When entering tumour thickness into the model, the RER raised to 0.70. Thus, the decrease in tumour thickness was sufficient to explain a substantial part of the improvement observed in 2008–2012, while accounting for less than 20% of the improvement occurring in 2013–2017.

For female patients (Table 4), the pattern of RER of death was roughly similar, but their values were all higher. Both in 2008–2012 and 2013–2017, and at all steps of the model, the risk of death was nonsignificantly lower than in 2003–2007.

Stepwise multivariate analysis of survival: sensitivity analysis

In the sensitivity analysis of the multivariate RER of death the total series of cases from the 17 674 patients was used. The

results are shown in Table S2 (male patients) and Table S3 (female patients, see Supporting Information). For male patients, both methods yielded results virtually equal to those of the basic analysis, in particular for the years 2013–2017. With respect to female patients, the RERs obtained after multiple imputation for the years 2013–2017, with an increased statistical power, were nearer to those obtained among male patients with the basic analysis (rose from 0.74, 95% CI 0.58–0.93, to 0.82, 95% CI 0.66–1.02), and had a borderline level of significance. This provided a post hoc confirmation that retaining female patients in the analysis was correct.

Discussion

The principal findings of this study can be summarized as follows. Firstly, we confirmed the strong prognostic significance of tumour thickness in Italian patients diagnosed with CMM in the past 20 years, we provided details of the time trend towards the diagnosis of thinner lesions and we documented the parallel trend towards improved survival. This supported the validity of the study rationale.

Secondly, we found that the decrease in tumour thickness among male patients explained largely the survival gain for patients diagnosed in 2008–2012 vs. those diagnosed in 2003–2007 but not the gain observed in 2013–2017. Both in the

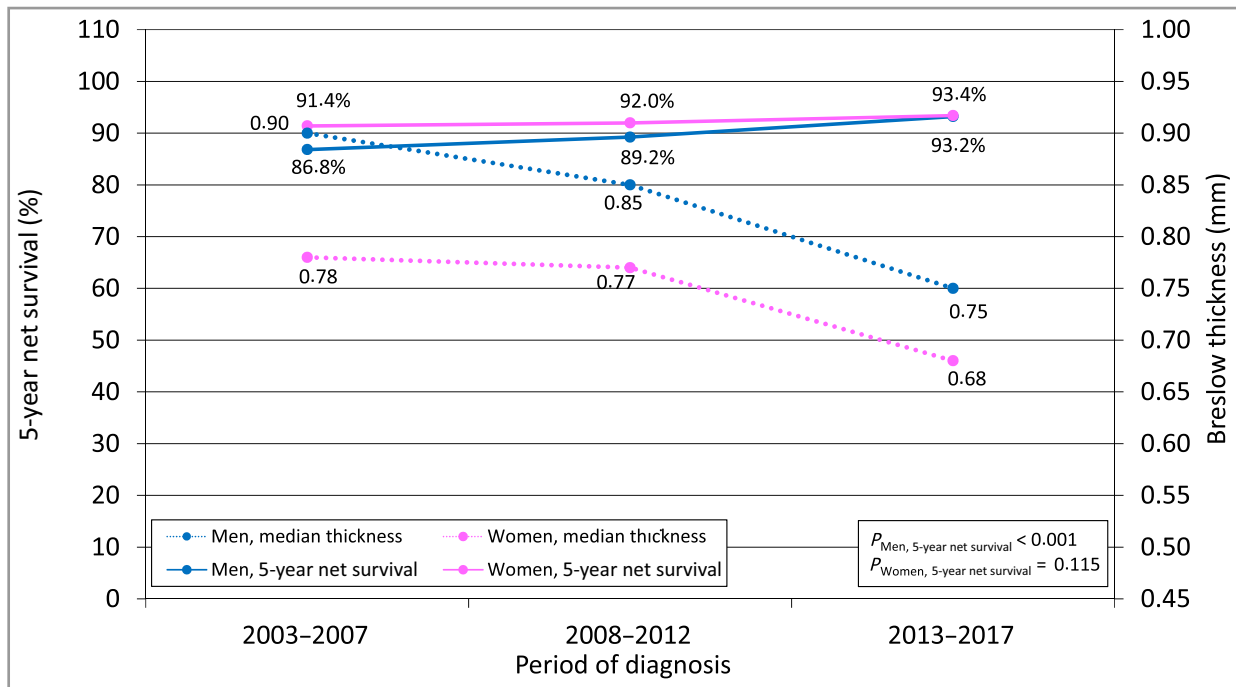


Figure 1 Time trend in median Breslow tumour thickness of cutaneous malignant melanoma and in 5-year per cent net survival from the disease, by sex, Italy, 2003–2017. Median tumour thickness was computed for those cases from patients for whom the numerical value of tumour thickness was found ($n = 14\,247$). Five-year net survival was computed for the ‘core subset’ of eligible patients ($n = 16\,130$), that is, those whose case could be categorized according to the American Joint Committee on Cancer staging criteria.³⁶ Five-year net survival was age-standardized using the International Cancer Survival Standard-2 weights.⁴⁰ P-values for trend are from a Poisson regression model for net survival including the time period of diagnosis as a numeric variable.

basic multivariate analysis (Table 4) and in the sensitivity analysis, the inclusion of tumour thickness in all three models caused the RER of death in the years 2013–2017 to increase from approximately 0.60 to 0.70. This means that the decrease in tumour thickness accounted for a smaller part of the survival improvement occurring in the period. The remaining component was because of another (or more than one) unmeasured correlate of the years 2013–2017 not included in the models.

Thirdly, given their better baseline data, the increasing time trend in survival among female patients did not reach a minimum standard level of significance. In 2013–2017, they had a minimally (nonsignificant) reduced risk of death. For patients diagnosed in this time period, however, the analysis of a dataset in which missing tumour thickness values were multiply imputed, thus increasing the statistical power, yielded a pattern of results comparable with that seen among male patients and with a borderline level of significance.

We believe that the interpretation of these results is straightforward. The marked survival gradient across tumour thickness categories confirmed the value of early detection of CMM, particularly among male patients. A persistent decrease in tumour thickness accounted for a part – albeit a lesser part – of the recent prognostic improvement, reflecting the high levels of sensitivity in CMM screening in Italy.⁴⁶ The potential benefit of early detection of the disease is well illustrated by the fact that male and female patients with thin CMM (i.e.

< 0.8 mm and 0.8–1.0 mm thick), had a 5-year net survival varying approximately between 100% and 102% (Table 1), that is, the same life expectancy as the general population or even a better one. This is equivalent to saying that they can be considered cured.⁴⁷

The great improvement in treatment strategies for CMM that have taken place in the past decade, with the approval of molecular targeted therapies and immune checkpoint inhibitors for unresectable and metastatic disease,²⁸ is the most likely factor accounting for the remaining – and greater – part of the survival gain achieved in 2013–2017. This is strongly suggested by two key considerations. Firstly, the two drugs that have changed substantially the way patients with advanced CMM are treated (i.e. ipilimumab and the targeted agent vemurafenib) were shown to improve survival in phase III trials of patients with metastatic CMM between 2010 and 2011^{48–50} and were approved by the Italian Drug Agency in the first half of 2013. This is shown in Figure S1 (see Supporting Information). And, secondly, not only was the upward trend in survival more pronounced among male patients, but this trend was even more pronounced for lesions in the two highest tumour thickness categories. This is in accordance with findings from basic and clinical research. The biological trait underlying the historical survival disadvantage of male patients with CMM is most likely to be host-related (with male patients having less resistance to progression)

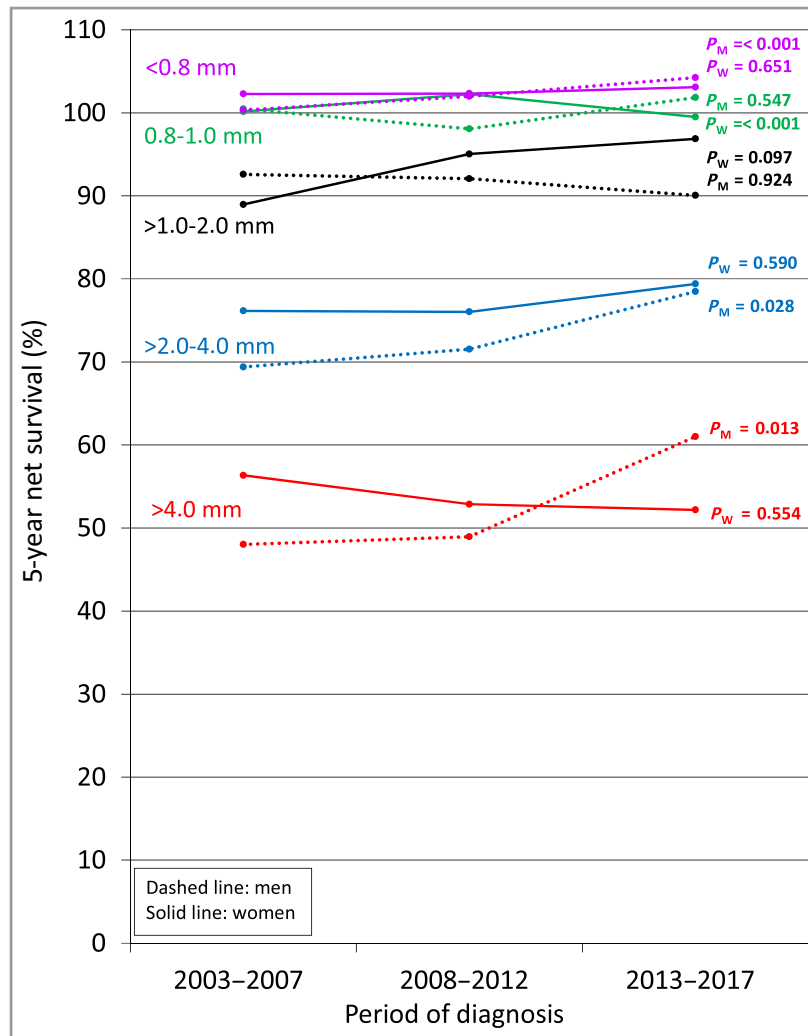


Figure 2 Time trend in tumour thickness category-specific 5-year per cent net survival from cutaneous malignant melanoma, by sex, Italy, 2003–2017. Tumour thickness was categorized according to the American Joint Committee on Cancer staging criteria.³⁶ Five-year net survival was computed for the ‘core subset’ of eligible patients ($n = 16\,130$), that is, those whose case could be categorized according to the above criteria. P-values for trend are from a Poisson regression model for net survival including the time period of diagnosis as a numeric variable. M, men; W, women.

rather than tumour-related (with male patients having more aggressive CMMs).^{51,52} Consequently, men with CMM benefit from a larger overall survival increase when treated with immune checkpoint inhibitors.^{53,54} This explains the crucial finding that male patients, for the first time in Italy, exhibited virtually the same net survival as female patients despite still being diagnosed with thicker lesions.

The results and the conclusions of this study are consistent with those of a recent study from the USA reporting data from 34 population-based cancer registries.²⁷ A pronounced improvement in short-term survival has occurred among patients diagnosed with metastatic CMM during the past decade. The authors have attributed this progress to the US Food and Drug Administration approval of targeted therapies and immune checkpoint inhibitors.

With respect to Europe, the real-world effectiveness of novel treatments has been assessed using single-institution and multicentre hospital-based CMM, or metastatic CMM,

registries.^{55–57} These studies have most often compared patients receiving novel treatments with patients undergoing conventional treatments. Except for the Netherlands and Denmark, where these institutions have nationwide coverage, the inclusion of all patients in hospital-based registries is challenging and the registered case series may be biased.⁵⁸ This highlights the importance of a population-based study like the present one. We used an intention-to-treat approach by considering the whole population of patients with CMM, whatever the extent to which they were actually and correctly treated.

This study also has limitations that need careful consideration. Firstly, cancer registration in Italy has been introduced irregularly both in time and space. The implications of, and the potential solutions to, this drawback are discussed in another article.²⁹ Restricting the analysis to a smaller number of registries with comparable time periods of registration, as we did in this study, is one of the most commonly used approaches.⁵⁹

Table 4 Multivariate relative excess risk (RER) of death from cutaneous malignant melanoma by time period of diagnosis, by sex, Italy, 2003–2017^a

Sex and model	LR test	P-value	RER (95% CI)		
			2003–2007	2008–2012	2013–2017
Male patients					
A, Time period			1.00	0.84 (0.67–1.06)	0.63 (0.48–0.82)
B, Model A plus patient age	B vs. A	< 0.001	1.00	0.83 (0.67–1.02)	0.59 (0.47–0.76)
C, Model B plus histological subtype	C vs. B	< 0.001	1.00	0.83 (0.68–1.01)	0.63 (0.50–0.79)
D, Model C plus tumour subsite	D vs. C	0.031	1.00	0.82 (0.67–1.00)	0.64 (0.51–0.80)
E, Model D plus tumour thickness	E vs. D	< 0.001	1.00	0.91 (0.76–1.09)	0.70 (0.57–0.86)
Female patients					
A, Time period			1.00	0.94 (0.69–1.28)	0.73 (0.50–1.06)
B, Model A plus patient age	B vs. A	< 0.001	1.00	0.93 (0.71–1.21)	0.72 (0.52–1.00)
C, Model B plus histological subtype	C vs. B	< 0.001	1.00	0.99 (0.77–1.28)	0.88 (0.65–1.19)
D, Model C plus tumour subsite	D vs. C	0.026	1.00	0.97 (0.75–1.25)	0.87 (0.65–1.18)
E, Model D plus tumour thickness	E vs. D	< 0.001	1.00	1.01 (0.81–1.27)	0.91 (0.70–1.18)

CI, confidence interval; LR, log-likelihood ratio. ^aThe RER of death is from a flexible parametric model for net survival with 5 degrees of freedom for male patients and 6 degrees of freedom for female patients. The number of degrees of freedom corresponds to the number of the model with the lowest Akaike information criterion. P-values are for the log-likelihood ratio test comparing each model with the previous one.

Secondly, we had no information on ulceration – a known adverse prognostic indicator. The main prognostic role of this feature, however, is to subcategorize tumour thickness, which remains the key histopathological determinant of survival.²² Also, ulceration is a marker of immunogenicity, and has been shown to be the key predictive marker of response to adjuvant interferon.⁶⁰ A comparable role in patients treated with immune checkpoint inhibitors has been hypothesized. In a trial of patients with resected stage III CMM, ulceration predicted patients' sensitivity to ipilimumab.⁶¹ After long-term follow-up, however, this finding was not confirmed.⁶²

Thirdly, we were not able to take account of potential overdiagnosis. However, it is very unlikely that the prevalence of overdiagnosis, which is associated with the intensity of dermatological screening, is greater among male patients, who still present with thicker lesions.

We conclude that, especially among male patients, the marked decrease in tumour thickness accounted for a small part of the recent improvement in survival observed in Italy. The introduction of targeted therapies and immunotherapies in the past decade is most likely to account for a much larger part of the improvement. This demonstrates that these treatments have the potential to have a measurable impact on the survival of patients, especially male patients, at the population level, and that the historical prognostic gap between men and women with CMM can be bridged. By implication, access to novel therapies should be ensured.

Acknowledgments

The authors thank Veronica Di Carlo (Cancer Survival Group, Department of Non-Communicable Disease Epidemiology,

London School of Hygiene and Tropical Medicine, London, UK) for her valuable comments.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Main characteristics of participating cancer registries, resident adult population, total number of patients with cutaneous malignant melanoma who were entered into the study, number excluded and number eligible. Italy, 2003–2017.

Table S2 Sensitivity analysis of the multivariate relative excess risk of death from cutaneous malignant melanoma by time period of diagnosis. Male patients (n = 9108), Italy, 2003–2017.

Table S3 Sensitivity analysis of the multivariate relative excess risk of death from cutaneous malignant melanoma by time period of diagnosis. Female patients (n = 8566), Italy, 2003–2017.

Figure S1 Time axis presenting the dates of approval of molecular targeted therapies and immune checkpoint inhibitors for the treatment of unresectable and metastatic cutaneous malignant melanoma by the US Food and Drug Administration, the European Medicines Agency and the Italian Drug Agency (Agenzia Italiana del Farmaco).

Video S1 Speech transcription.