

DECREASING THICKNESS AND ENHANCED THERAPY HAVE BOTH CONTRIBUTED TO THE 2010s INCREASE IN SURVIVAL FROM MELANOMA IN ITALY

Federica Zamagni (1), Lauro Bucchi (1), Silvia Mancini (1), Emanuele Crocetti (1), Luigino Dal Maso (2), Stefano Ferretti (3), Flavia Baldacchini (1), Orietta Giuliani (1), Alessandra Ravaoli (1), Rosa Vattiato (1), Annibale Biggeri (4), Simona Villani (5), Angelita Brustolin (6), Giuseppe Candela (7), Giuliano Carrozzi (8), Ylenia Maria Dinaro (9), Margherita Ferrante (10), Silvia Iacovacci (11), Carla Masini (12), Guido Mazzoleni (13), Maria Michiara (14), Sante Minerba (15), Silvano Piffer (16), Umberto Scala (17), Diego Serraino (2), Fabrizio Stracci (18), Rosario Tumino (19), Giuseppe Palmieri (20), Ignazio Stanganelli (21), Fabio Falcini (1, 22)

BACKGROUND

After World War II, the incidence of cutaneous malignant melanoma (CMM) has increased in the whole western world. This trend has resulted from a change in sunbathing habits towards a more intermittent and intense ultraviolet radiation exposure coupled with an increased use of artificial ultraviolet radiation sources. The incidence increase has been primarily driven by early-stage CCM cases, defined as having a small Breslow tumour thickness (a small distance between the most superficial layer of the skin to the deepest level of invasion). The incidence of thick CMM has also increased, but less. The Breslow-thickness-specific incidence trends have been paralleled by an increase in survival in many countries. As a low Breslow thickness is the single most favourable prognostic factor, researchers have generally related the survival increase to the rise in thin CMM incidence rates. This temporal correlation, however, is not necessarily evidence for a causal and exclusive link. In view of their potential implications on policies for secondary prevention and treatment of CMM on a public health scale, these observations need to be confirmed in other populations.

OBJECTIVE

This study aimed to determine the relative role that the improvement in tumour thickness has played in the favourable trend in survival from CMM in the adult Italian population (age ≥ 15 years) over the last two decades.

METHODS

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. Eleven local cancer registries provided data for primary CMM cases registered between 2003 and 2017 ($n=17674$). Age standardised 5-year net survival (NS) was calculated with the non-parametric Pohar Perme estimator using the *strs* STATA command and the International Cancer Survival Standard type 2 weights. To assess the trends in the incidence of CMM by prognostic features, we obtained the estimated average annual percent change (EAAPC) by fitting a generalised linear regression model for the natural logarithm of the age-standardised incidence rates and year as a linear trend, with a Gaussian distribution and identity link function. Multivariate analysis of 5-year NS was done by calculating the relative excess risk of death (RER). The excess risk of death is the risk above the one which would have been observed if the population death rates had been applied to the cancer patients. The relative contribution of the decrease in tumour thickness to the trend in RER was evaluated with a forward stepwise analysis, based on flexible parametric models fitted on the log cumulative excess hazard scale with the *stmp2* STATA command. The number of degrees of freedom (5 and 2 for men and women, respectively) was chosen using the Akaike Information Criterion (AIC).

RESULTS

- ❖ Tumour thickness is inversely associated with 5-year NS and multivariate RER in both genders over the whole study period.
- ❖ The incidence rose more rapidly for thin CMM (0 to 1 mm thick) than for the two intermediate thickness categories (Table 1). These trends combined left to a decrease in the median tumour thickness for both genders. Median tumour thickness was 0.90 mm in 2003-2007, 0.85 mm in 2008-2012 and 0.75 mm in 2013-2017 among men, and 0.78 mm, 0.77 mm and 0.68 mm among women.
- ❖ 5-year NS was 89.4%, 90.7% and 95.2% among men and 92.9%, 93.5%, and 95.2% among women, respectively.
- ❖ For both genders, the increasing survival trend was more pronounced with increasing tumour thickness (Figure 1).

AFFILIATIONS

(1) Romagna Cancer Registry, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy; (2) Cancer Epidemiology Unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy; (3) Romagna Cancer Registry, section of Ferrara, Local Health Authority, and University of Ferrara, Ferrara, Italy; (4) Department of Statistics, Computer Science, Applications G. Parenti, University of Florence, Florence, Italy; (5) Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy; (6) UOC PreSAL-Dipartimento di Prevenzione ASL Viterbo, c/o Cittadella della Salute, Viterbo, Italy; (7) Trapani Cancer Registry, Dipartimento di Prevenzione della Salute, Servizio Sanitario Regionale Sicilia, Azienda Sanitaria Provinciale (ASP), Trapani, Italy; (8) Modena Cancer Registry, Public Health Department, Local Health Authority, Modena, Italy; (9) Siracusa Cancer Registry, Health Unit of Siracusa, Italy; (10) Integrated Cancer Registry of Catania-Messina-Enna, Azienda Ospedaliero-Universitaria Policlinico "Rodolico-San Marco", Catania, Italy; (11) Latina Cancer Registry, Lazio, Italy; (12) Unit of Oncological Pharmacy, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy; (13) South-Tyrol Tumor Registry, Bolzano, Italy; (14) Parma Cancer Registry, Medical Oncology Unit, University Hospital of Parma, Parma, Italy; (15) Registro tumori di Taranto, Unità operativa complessa di statistica ed epidemiologia, Azienda sanitaria locale Taranto, Italy; (16) Trento Province Cancer Registry, Unit of Clinical Epidemiology, Trento, Italy; (17) Cancer Registry - ASL Salerno, Salerno, Italy; (18) Public Health Section, Department of Experimental Medicine, University of Perugia, Perugia, Italy; (19) Cancer Registry and Histopathology Department, Provincial Health Authority (ASP), Ragusa, Italy; (20) Institute of Research on Genetics and Biomedicine (IRGB), National Research Council (CNR), Sassari, Sardegna, Italy; (21) Skin Cancer Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy; (22) Cancer Prevention Unit, Local Health Authority, Forlì, Italy

- ❖ Men: the inclusion of tumour thickness into the forward stepwise flexible parametric model (Table 2) made the RER in 2013-2017 versus 2003-2007 to increase from 0.62 (95% CI, 0.48-0.82) to 0.69 (0.54-0.87).
- ❖ Women: the results were not significant. By including cases with unknown tumour thickness, the RER rose from 0.78 (0.55-1.12) to 0.83 (0.62-1.11) (Table 2). In a sensitivity analysis, however, results were more similar to those obtained among men: the inclusion of tumour thickness into the forward stepwise model made the RER in 2013-2017 versus 2003-2007 to increase from 0.74 (0.59-0.94) to 0.83 (0.66-1.04).

Table 1. Average annual cutaneous malignant melanoma incidence rates per 100,000 persons and estimated average annual percent change by tumour thickness, by sex. Italy, 2003-2017.

Thickness (mm)	Men		Women	
	ASIR (95% CI)	EAAPC (95% CI)	ASIR (95% CI)	EAAPC (95% CI)
0-1	10.7 (10.4-11.1)	6.7* (5.7-7.8)	10.4 (10.1-10.6)	4.7* (3.4-6.0)
1.01-2	2.9 (2.7-3.0)	3.1* (1.6-4.5)	2.3 (2.2-2.4)	1.6* (0.4-2.9)
2.01-4	2.2 (2.0-2.3)	3.2* (1.9-4.4)	1.3 (1.2-1.4)	3.1* (1.3-4.8)
>4	2.1 (1.9-2.2)	4.9* (3.4-6.4)	1.1 (1.0-1.2)	5.0* (2.7-7.2)

ASIR, age-standardised incidence rate; CI, confidence interval; EAAPC, estimated average annual percent change. *Significantly different from zero at the alpha level of 0.05.

Figure 1. Time trend in tumour thickness category-specific 5-year percent net survival from cutaneous malignant melanoma, by sex. Italy, 2003-2017.

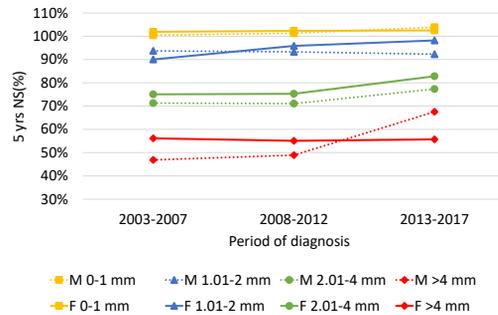


Table 2. Multivariate relative excess risk of death from cutaneous malignant melanoma according to time period of diagnosis, by sex. Italy, 2003-2017.

Sex	Model Variable	LR Test P-value	RERs and 95% CI		
			2003-2007	2008-2012	2013-2017
Men	A Period		1.00	0.93 (0.71-1.21)	0.64 (0.46-0.87)
	B Model A + age	B vs A <0.001	1.00	0.89 (0.70-1.14)	0.60 (0.45-0.80)
	C Model B + histologic subtype	C vs B <0.001	1.00	0.87 (0.69-1.10)	0.61 (0.46-0.80)
	D Model C + subsite	D vs C 0.034	1.00	0.86 (0.68-1.09)	0.62 (0.48-0.82)
	E Model D + thickness	E vs D <0.001	1.00	0.93 (0.76-1.14)	0.69 (0.54-0.87)
Women	A Period		1.00	0.95 (0.66-1.37)	0.64 (0.40-1.01)
	B Model A + age	B vs A <0.001	1.00	0.94 (0.69-1.29)	0.65 (0.44-0.97)
	C Model B + histologic subtype	C vs B <0.001	1.00	0.97 (0.72-1.30)	0.78 (0.55-1.12)
	D Model C + subsite	D vs C 0.077	1.00	0.96 (0.71-1.29)	0.78 (0.55-1.12)
	E Model D + thickness	E vs D <0.001	1.00	0.99 (0.77-1.27)	0.83 (0.62-1.11)

LR, likelihood ratio; RER, relative excess risk; CI, confidence interval.

CONCLUSIONS

The marked decrease in tumour thickness accounted for a small part of the improvement in survival observed in 2013-2017. The introduction of molecular targeted therapies and immune checkpoint inhibitors for unresectable and metastatic disease, is the most likely factor accounting for the remaining component of the survival gain. Particularly, ipilimumab and vemurafenib, which have changed the way patients with advanced melanoma are treated, have been approved by the Italian Drug Agency in the first half of 2013, i.e. the initial year of the last 5-year time period considered in this study.