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SPECIAL ARTICLE

The descriptive epidemiology of melanoma in Italy has changed — for the better

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ABSTRACT

A recent research project using data from a total of 40 cancer registries has provided new epidemiologic insights into the results of efforts for melanoma control in Italy between the 1990s and the last decade. In this article, the authors present a summary and a commentary of their findings. Incidence increased significantly throughout the study period in both sexes. However, the rates showed a stabilization or a decrease in men and women aged below 35 years. The risk of disease increased for successive cohorts born until 1973 (women) and 1975 (men) while subsequently tending to decline. The trend towards decreasing tumor thickness and increasing survival has continued, but a novel favorable prognostic factor has emerged since 2013 for patients — particularly for males — with thick melanoma, most likely represented by molecular targeted therapies and immune checkpoint inhibitors. Due to this, the survival gap between males and females has been filled out. In the meanwhile, and despite the incidence increase, dermatologists have not lowered their threshold to perform skin biopsy. Skin biopsy rate has increased because of the increasingly greater volume of dermatologic office visits, but the proportion of skin biopsies out of dermatologic office visits has remained constant. In summary, an important breakthrough in melanoma control in Italy has taken place. Effective interventions have been implemented across the full scope of care, which involve many large local populations — virtually the whole national population. The strategies adopted during the last three decades represent a valuable basis for further steps ahead in melanoma control in Italy.

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KEY WORDS: Melanoma; Epidemiology; Incidence; Survival.

In 2018, the Romagna Cancer Registry (which has subsequently become part of the Emilia-Romagna Cancer Registry) developed a multicenter cancer registry-based research project to update the epidemiologic trends of cutaneous malignant melanoma – hereby briefly referred to as melanoma – in Italy. The project, funded by the Italian Melanoma Intergroup and the Ministry of Health (*Ricerca Corrente*), has generated three main published articles reporting novel and important findings about the time trends in overall and Breslow tumor thickness-specific incidence and survival, in dermatologic office visit rate and in skin biopsy rate.[1-3] This information offers new epidemiologic insights into the results of national efforts for melanoma control. Here, we present a summary and a commentary of the multifaceted and interrelated results of the three studies. Our objective is to increase their dissemination among the practicing dermatologists. Ancillary investigations that are still ongoing will add further details, but will not change the overall scenario described in this article.

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

Incidence

First of all, and most importantly, the project has had the unique opportunity to take a snapshot of the exact moment in which the long-term relentless incidence increase of melanoma has started to slow down. Since approximately World War II, melanoma rates have increased for several decades in virtually all Caucasian populations of the world.[1, 4-9] This was because of the widespread adoption of sunbathing, with an intermittent and more intense ultraviolet radiation exposure without protection,[10, 11] and the concomitant increase in the use of indoor tanning beds. The uptrend took place as a well-defined birth-cohort-dependent incidence change. The new sun exposure habits were first adopted by generations born in a period of some decades before and, in part, after World War II depending on the country and, with an ever-increasing prevalence, by subsequent generations. In its early phases, the change had no influence whatsoever on incidence at the whole population level, because it was confined to limited subgroups of people who had a still low absolute risk of disease. Over time, however, these incoming birth cohorts at higher and higher risk of melanoma grew old and replaced the earlier ones. The interaction between the epidemiologic change and the demographic dynamics boosted the overall incidence trend. This peculiar progression of the risk of melanoma through the population was described as an epidemic.

Approximately around the end of the last century, however, the increasing trend began to slow down and then to plateau in most countries, finally followed by a decline of rates.[6, 11-16] The turning point, for example, was reached around 1990 in Australia and about 10 years later in the USA. Like the previous upward trend, the reversal too evolved as a birth-cohort-dependent phenomenon, even though in the opposite direction. In Australia, for example, the risk of melanoma peaked for men born before 1930, levelled-off in the birth cohorts of 1930 to 1950, and decreased in those born subsequently. A closely comparable pattern of incidence was observed among women, though approximately five years earlier.[14, 15, 17, 18] In the USA, the risk increased constantly for successive cohorts

of non-Hispanic whites born between 1921 and 1981 and then began to decline.[19] As a consequence, the incidence rates stabilized before the turn of the century for people younger than 50-60 years.[13] In the following decade, a significant decrease was finally observed among young adults.[20]

As far as Europe is concerned, the uptrend in incidence started in north-western countries and spread over time to lower latitudes.[6, 21] In north-western Europe, the increase in incidence has been strong until the 1980s, after which the rates have stabilized or declined starting from the cohorts of 1930 to 1940.[6] Until recently, instead, the turning back of the incidence trend had not yet occurred in southern,[22-24] south-western[25, 26] and south-eastern Europe.[27] The only exceptions are two anecdotal regional studies reporting a decreasing incidence in Catalonia for people aged 25-29 years in the first decade of this century[28] and a slight decrease in the Emilia-Romagna Region (northern Italy) among women born after 1961, coupled with an attenuation of the uptrend in the latest cohorts of men.[29]

The first study carried out within our research project provided formal evidence that the reversal of the long-term incidence trend of melanoma has begun to extend to Italy.[1] Data were obtained from 38 local cancer registries, that are listed in Supplementary Digital Material 1 (Supplementary Table I). After considering their different time periods of registration, 21 of them were selected that covered to a satisfactory extent the years 1994-2013. At the mid-point of this time interval (2003), the population was 15,814,455, equivalent to 27.5% of Italians. The number of melanoma cases registered during the period was 45,264. Figure 1 shows the registration areas and summarizes the average annual age-standardized incidence rates in the years 2009-2013, the most recent 5-year period covered by the study. The trends in age-standardized rates were analyzed using joinpoint regression models and age-period-cohort models.

The estimated age-standardized incidence rates confirmed the upward trend of previous decades, with a constant and significant increase by an annual 3.6% (men) and 2.5% (women). Five-year age-specific rates, however, showed a stabilization or a decrease in men and women aged less than 35 years. Finally, the analysis of trends by birth cohort (Figure 2) revealed an increasing incidence for all successive cohorts born until 1973 (women) and 1975 (men), followed by a decline for those born later.

These are the earliest manifestations of a birth-cohort-dependent decrease in the risk of melanoma in Italy. They demonstrate that the latest generations of Italians have adopted safe sun exposure habits[16] and this, in turn, indicates that sun protection education has been effective in influencing their behaviour. Most likely, these generations are

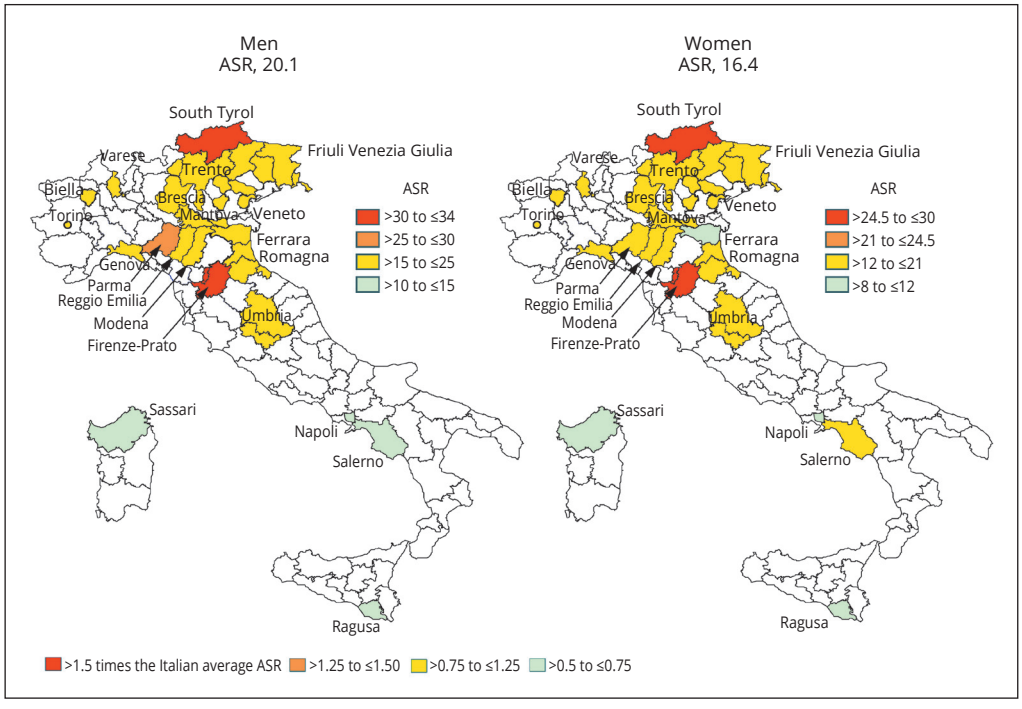

Figure 1.—Absolute and categorized average annual age-standardized (2013 European standard population) incidence rate (per 100,000) of cutaneous malignant melanoma in Italy from 2009 to 2013, *i.e.*, the most recent 5-year period of data contribution, by sex and cancer registration area. ASR indicates age-standardized rate. ASRs are categorized according to their ratio to the Italian average ASR (modified from Bucchi *et al.*).[1]

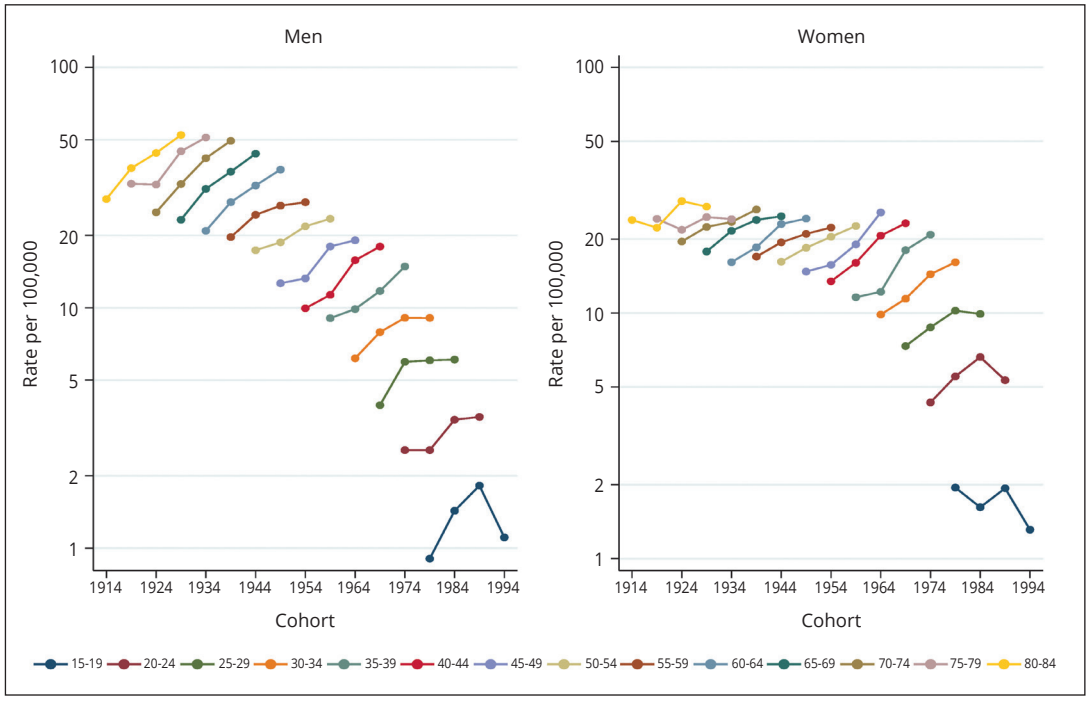

Figure 2.—Five-year age-specific incidence rate (per 100,000) of cutaneous malignant melanoma in Italy from 1994 to 2013 on a semi-logarithmic scale, by sex and 10-year birth cohort (population aged 15-84 years). The rates for each age group are joined by lines and are plotted against the mid-year of birth (modified from Bucchi *et al.*).[1]

those who have been targeted by sun protection messages from the childhood, which may involve an educational role of parents and is known to enhance the preventive impact.[18] The authors have put forward a second, and most likely complementary, hypothesis to explain their results: they have suggested that melanoma information campaigns have started having an impact on sun exposure habits in those birth cohorts in whom the increase in incidence of disease has caused a sufficient level of public alarm.[29] Following this line of reasoning, the more recent onset of the melanoma epidemic in Italy compared with other western countries[21] and the lower baseline rates would explain well why education campaigns have succeeded later. In any case, the educational effort should be maintained and strengthened. In other western countries, further explanations for the avoidance of excessive sun exposure in the most recent cohorts have been added including, in particular, an increase in indoor leisure activities (for example, using computers).[18] It must be considered, however, that the percentage of leisure time spent using computers by young Italians is among the lowest in Europe and that the percentage spent outdoors is still the highest.[30]

The down-turn in incidence that starts being observed in Italy will evolve in a predictable manner. It can be expected that the sun avoidance behaviour adopted by the most recent generations covered by this study will persist or, more likely, will strengthen in the next ones, as is confirmed by a survey of children showing that the reported prevalence of recent and total sunburn episodes has further decreased in the first two decades of this century.[31] These cohorts will get old and will gradually replace the cohorts who have experienced higher levels of sun exposure. Finally, the changing epidemiologic composition of the population will have an impact on the overall risk of melanoma, although reasonable estimates of future rates and rate changes are premature and will require accurate projections of the age structure and growth patterns of Italians. Aside from this, it is likely that the elderly will be increasingly represented in the population for years. Since they will continue to have a high risk of disease, the average age at diagnosis of melanoma will inevitably become higher. A comparable age shift and the associated clinical consequences have already accompanied for decades, particularly in northern Italy, another declining epidemic: that of gastric cancer.[32]

Survival

The endpoint of the second published study from the Italian research project, by Zamagni *et al.*,[2] was 5-year net survival (NS). NS is defined as the probability to survive cancer in the absence of other causes of death. By implication, NS is not influenced by cross-sectional differences and temporal

changes in mortality from other causes. Closely related to the long-term incidence increase seen in Italy and elsewhere was an upward trend in the prognosis of melanoma, as described in many previous studies.[33, 34] The overwhelming majority of investigators have attributed this improvement to the common observation that the incidence increase was mostly accounted for by early or thin melanomas,[14, 35-37] generally defined as having a thickness ≤1.00 mm.[14, 35-37] The trend towards decreasing tumor thickness was the plausible result of a growing public awareness of the early signs of the disease coupled with an increased sensitivity of dermatologic screening.[38] The trend to earlier detection and tumor downstaging led to a decreased incidence of rapidly fatal melanomas (associated to death within one to three years of diagnosis)[39] as well as a phenomenon of overdiagnosis,[38, 40] defined as the detection of melanomas that would not progress nor surface clinically over the patient's lifetime. Both contributed to the survival improvement.

Some studies, however, have questioned the exclusive role of the increasingly earlier detection of melanoma in determining this outcome.[41, 42] In particular, recent data from the USA have shown a survival gain in all tumor thickness categories,[43] including the thickest ones and the metastatic disease,[36] as a very likely consequence of the introduction of molecular targeted therapies and immune checkpoint inhibitors in the last decade.[44] In order to obtain a confirmation or a rejection of this hypothesis for the Italian population, we have investigated, first, the relationship between the temporal trend in tumor-thickness-specific incidence and the trend in survival from melanoma in Italy and, second, the relative role of changes in tumor thickness in the improvement in survival.

The study was proposed to those local cancer registries which were able to provide information on tumor thickness, usually not included among registration variables. Eleven were eligible (Supplementary Digital Material 1: Supplementary Table I). None of these registries has collected information on systemic treatment. They provided records of incident melanoma cases with a date of diagnosis between 2003 and 2017. In 2010, they covered a population of 8,056,608. The total number of eligible cases was 17,674. Of these, 16,130 (91.3%) could be categorized by tumor thickness according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging criteria.[45] Age standardized 5-year NS was calculated. Multivariate analysis of 5-year NS was performed by calculating the relative excess risk of death (RER). The contribution of the decrease in tumor thickness to the change in RER was assessed using a forward stepwise flexible parametric survival model that included the available prognostic factors.

The key findings were as follows. First, the prognostic value of tumor thickness was confirmed. Over the entire study period, indeed, tumor thickness was inversely associated with 5-year NS as well as multivariate RER both among men and women. Second, the incidence rose especially among melanomas <0.8 mm thick (the largest category) and, consequently, the median tumor thickness decreased from 0.90 mm in 2003-2007 to 0.75 mm in 2013-2017 among men, and from 0.78 mm to 0.68 mm among women (Figure 3). Third, the 5-year NS grew from

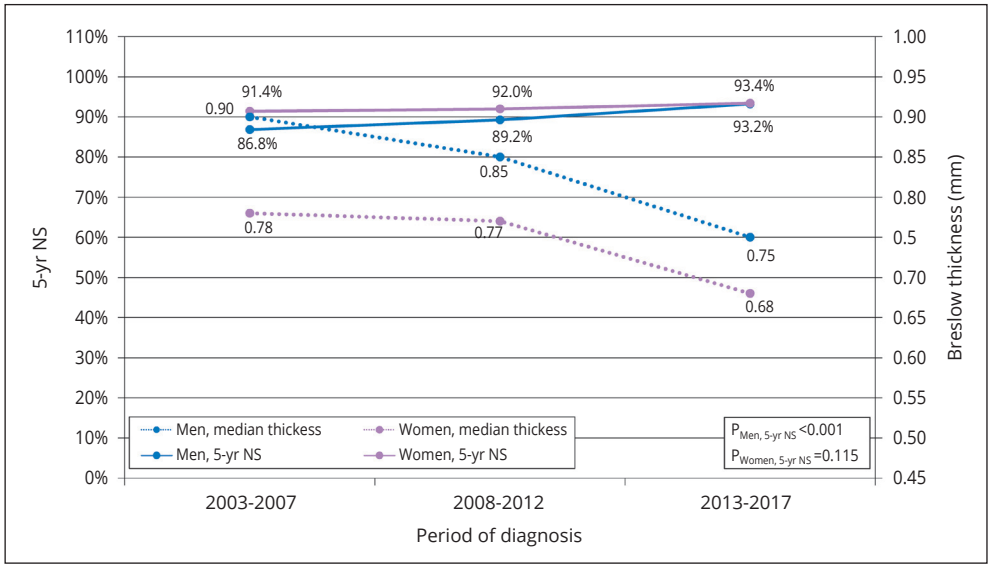

Figure 3.—Time trend in median Breslow tumor thickness of cutaneous malignant melanoma and in 5-year percent net survival (NS) from the disease in Italy from 2003 to 2017, by sex. Cutaneous malignant melanoma was defined as ICD-10 codes C43.0-C43.9. Median tumor thickness was computed for those cases for whom the numerical value of tumor thickness was found (n = 14,247). Five-year net survival was computed for the subset of eligible cases who could be classified into the five American Joint Committee on Cancer staging criteria[45] (N.=16,130). Five-year net survival was age-standardized using the International Cancer Survival Standard-2 weights. P-values for trend are from a Poisson regression model for net survival including the time period of diagnosis as a numeric variable (modified from Zamagni *et al.*).[2]

86.8% to 93.2% for men and from 91.4% to 93.4% for women, which is equivalent to saying that men diagnosed with melanoma in 2013 and after have survived as long as women despite continuing to have thicker lesions. Fourth, their increasing survival trend was more pronounced with increasing tumor thickness (Figure 4). And last, the forward stepwise model revealed that the thickness trend explained only in part, approximately 20%, the survival improvement of male patients. For women, the role of tumor thickness was not significant.

It clearly appears that the persistent trend towards earlier detection has not been the main driver of the survival improvement observed in the study period. Another, and stronger, prognostic factor has entered the scene of melanoma control in 2013, which is particularly beneficial for men and among the thickest melanomas. Despite the unavailability of population-based data on systemic treatments, these characteristics fit well with the profile of molecular targeted therapies and immune checkpoint inhibitors.[44] Ipilimumab and the targeted agent vemurafenib,

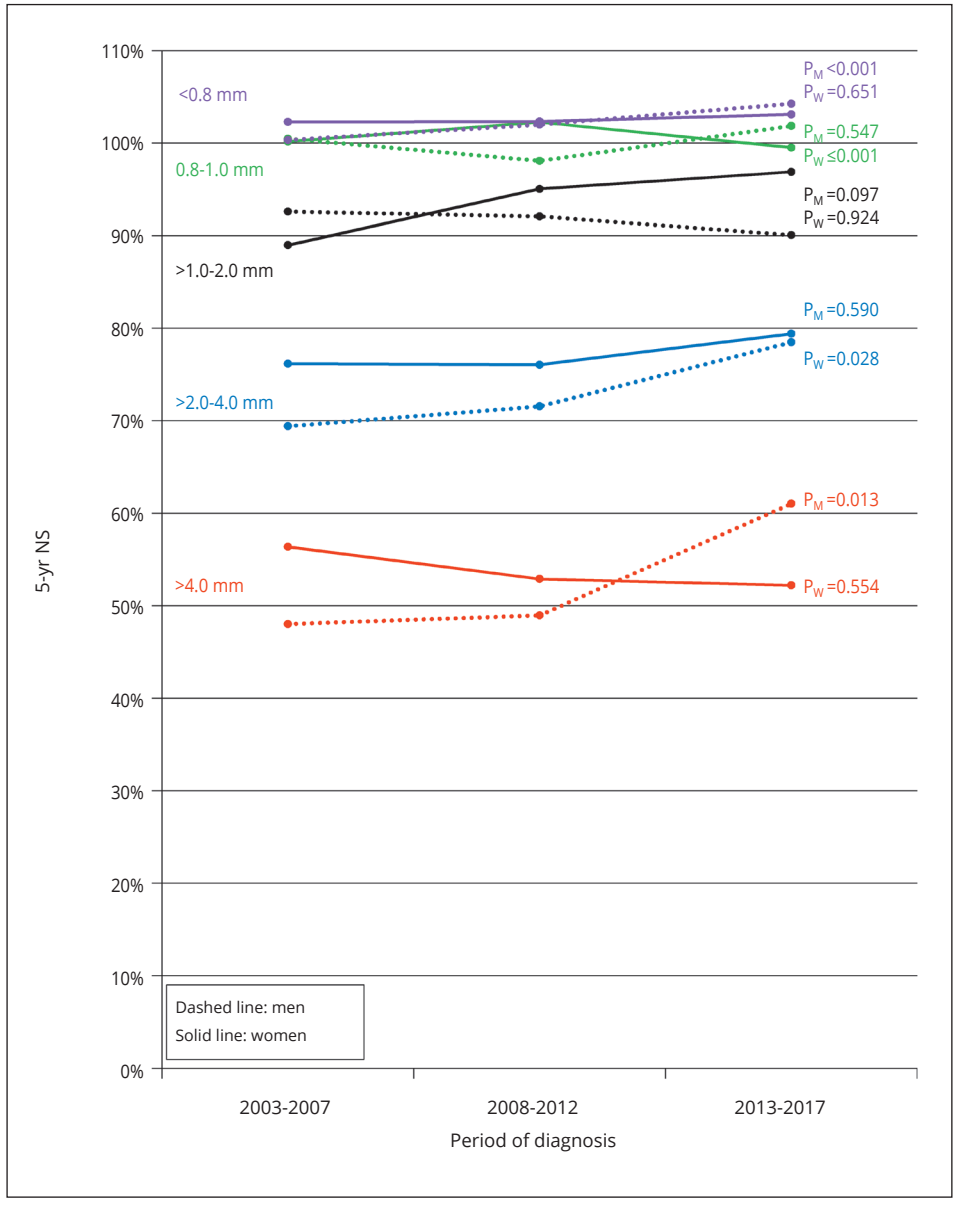

Figure 4.—Time trend in tumor thickness category-specific 5-year percent net survival from cutaneous malignant melanoma in Italy from 2003 to 2017, by sex. Cutaneous malignant melanoma was defined as ICD-10 codes C43.0-C43.9. Tumor thickness was categorized according to the American Joint Committee on Cancer staging criteria.[45] Five-year net survival was computed for the subset of eligible cases (N.=16,130) who could be classified into the five American Joint Committee on Cancer staging criteria (N.=16,130). P values for trend are from a Poisson regression model for net survival including the time period of diagnosis as a numeric variable (modified from Zamagni *et al.*).[2]
M: men; W: women.

in particular, were approved by the Italian Drug Agency (AIFA) in the first half of 2013. The results and the conclusions of this study are consistent with those of a multicenter, cancer registry-based study from the USA.[43]

The efficacy of targeted therapies and immune checkpoint inhibitors under ideal, controlled conditions has been demonstrated in phase III randomized controlled trials.[46] The above study may be considered a large-scale, intention-to-treat effectiveness study that confirms the efficacy of novel medications under real-world clinical conditions, *i.e*. under the usual circumstances of healthcare practice and considering the whole population of patients, whatever the extent to which they were actually and correctly treated. The results of the study, in fact, were far from being expected. In many instances, the advances in cancer treatment – albeit of experimentally proven efficacy – have no clear and recognizable impact on patient survival at the general population level. By implication, the study suggests that the medical treatment of melanoma in Italy is characterized by appreciable levels of accessibility to the state-of-the-art therapy and of appropriateness in its clinical uses, probably coupled with a good comparability between routine Italian patients and patients enrolled in clinical trials.

The newly acquired information on the trends in survival from melanoma in Italy adds to recent registry-based data on the trends in prevalence. The number of persons living after a diagnosis of melanoma has risen from 102,500 in 2010 to approximately 170,000 persons in 2020.[47] Also, the proportion of prevalent patients who have reached the same death rates as the general population of the same sex and age and, for this reason, can be considered to be virtually cured has grown to 75% for males and over 80% for females.[48]

Dermatologic office visit rate and skin biopsy rate

The hypothesis that an increasing public information and the diffusion of newer diagnostic technologies would be associated with overdiagnosis of melanoma and that the latter, in turn, would be largely responsible for the incidence trend was first supported by incidence trend data by tumor thickness.[14, 35-37]

The idea linking incidence trend to overdiagnosis was further corroborated by studies investigating skin biopsy data. In the USA, Welch *et al.* found a linear relation between the increasing incidence of early melanoma between 1986 and 2001 and an increase in skin biopsy rates, with mortality rates remaining stable.[49] They interpreted the increased volume of diagnoses of melanoma to be primarily the consequence of a greater diagnostic scrutiny, defined as the combined effect of more skin examinations, lower clinical threshold to biopsy, and lower threshold for pathologists to report a melanoma. An update to 2015 has confirmed the early data.[50] Another American study of similar design has reported an association between skin biopsy rates and incidence of in situ melanoma.[51]

This has suggested the third round of the Italian research project.[3] The authors have explored the ecological association between the trends in annual dermatologic office visit rates, skin biopsy rates, incidence rates of in situ and early invasive melanoma, and mortality rates from melanoma over the last two decades. The trends in patient presentation have never been evaluated in any previous study on the relationship between increased diagnostic scrutiny and the rising incidence of melanoma.

The study was restricted to four cancer registries situated in the Emilia-Romagna Region (Supplementary Digital Material 1: Supplementary Table I) because the project coordinating center had direct access to the regional outpatient care database (Italian: *Assistenza Specialistica Ambulatoriale* or ASA), which is made up of individual records of services delivered to non-admitted, non-emergency patients in outpatient clinics of the National Health Service. The four registries had data for ≥10 consecutive years of registration between 2003 and 2017, mortality data for the registration period, incidence data for in situ melanoma, and tumor thickness information. On 1 January 2010, the total resident population was 2,696,000. A series of 11,679 melanoma cases was studied. The dataset extracted from the Regional ASA database included 4,593,988 dermatologic office visits and 849,343 skin biopsies. Multiple skin biopsies from a single patient, performed during one or more dermatologic office visits, were included. All annual rates were age-standardized (2013 European standard population). Trends were described with the estimated average annual percent change. Correlations were tested with the Spearman correlation coefficient.

The Emilia-Romagna regional data confirmed the national pattern of incidence trends, with an increase in overall rates that was more pronounced for in situ melanoma, followed by melanoma <0.8 mm thick. Moderate but significant increases for most subgroups of melanomas ≥0.8 mm thick were observed. Mortality has been declining and significantly so among women. The annual rate of dermatologic office visits correlated with the annual rate of skin biopsy. Both showed an increase between 2003 and 2017. In turn, the annual rate of both dermatologic investigations

combined correlated with the annual incidence rates of in situ melanoma and early invasive melanoma, even though only among men.

The key finding, however, was that the annual proportion of the number of skin biopsies out of the number of dermatologic office visits was fairly constant over the study years, fluctuating between 18% and 22% among males and between 16% and 19% among females. Also, given the increasing prevalence of disease among patients attending dermatologic offices, the annual proportion of histologic confirmation of situ/invasive melanoma out of the number of skin biopsies – albeit low – rose over time. According to the authors, this is explained by the diffusion of dermoscopy in Italy,[52] which should be further expanded.

In summary, the increasing melanoma incidence trend is, at least in part, genuine, although it cannot be excluded that overdiagnosis may partly contribute. If so, however, overdiagnosis would be caused by an increased patient presentation at dermatologic offices and not by a lower clinical threshold to biopsy. This study support the idea that the rising incidence of melanoma has promoted both patient self-referral and primary care physician referral for dermatologic screening. In other words, as noted by Weinstock *et al.*,[51] the increase in biopsy rates might be the consequence of the increasing incidence, rather than its cause.

This interpretation, however, warrants further testing. The analysis was limited by the lack of information on the proportion of patients attending private dermatology clinics and on the proportion of skin biopsy specimens examined by a dermopathologist, which may have changed over time. Also, the issue of generalizability of results to other national contexts should be taken into account, because many healthcare system variables may interact with the public's health behaviour as well as the clinical threshold to biopsy and the pathologist's threshold to label an abnormality as malignant.

Conclusions

The results of this research project illustrate well that an important breakthrough in melanoma epidemiology and melanoma control in Italy has taken, and is still taking, place. They show that effective interventions have been implemented across the full scope of care, from primary prevention to early detection and treatment. Advances of different nature have occurred in a relatively brief time span. More importantly, it appears that these changes are involving numerous large local populations. The long-awaited birth-cohort-dependent decrease in the risk of disease is the key event, the only capable to reduce in the long run the burden of incidence. While the trend towards decreasing tumor thickness and increasing survival has continued, a novel favorable prognostic factor has emerged since 2013 for patients – in particular for males – with thick melanoma, most likely represented by molecular targeted therapies and immune checkpoint inhibitors. Due to this, the survival gap between males and females has finally been filled out, and the landscape of melanoma control has broadened. In the meanwhile, and despite the incidence increase, dermatologists have not lowered their threshold to perform skin biopsy. Skin biopsy rate has increased because of the increasingly greater volume of dermatologic office visits, which was probably due to the growing public alarm for the melanoma epidemic, while the proportion of skin biopsies out of dermatologic office visits remained constant. Although the hypothesis that a degree of overdiagnosis contributed to incidence trends remains valid, the role of dermatologists needs to be considered from a different angle. We conclude that the strategies adopted between the 1990s and the last decade represent a valuable basis for further steps ahead in melanoma control in Italy.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Lauro Bucchi conceived this article and drafted the manuscript. Silvia Mancini, Federica Zamagni and Annibale Biggeri analyzed the data. Francesca Bella, Ettore Bidoli, Adele Caldarella, Giuseppa Candela, Simona Carone, Giuliano Carrozzi, Rossella Cavallo, Margherita Ferrante, Stefano Ferretti, Rosa A. Filiberti, Mario Fusco, Luciana Gatti, Alessio Gili, Silvia Iacovacci, Michele Magoni, Lucia Mangone, Guido Mazzoleni, Maria Michiara, Antonino Musolino, Silvano Piffer, Daniela Piras, Roberto Vito Rizzello, Massimo Rugge, Umberto Scala, Giovanna Tagliabue, Federica Toffolutti, and Rosario Tumino collected and processed the data. Emanuele Crocetti, Luigino Dal Maso, Flavia Baldacchini, Rosa Vattiato, Orietta Giuliani, Alessandra Ravaioli, Stefano Rosso, Fabrizio Stracci, Carla Masini, Laura Ridolfi, Simona Villani, Giuseppe Palmieri, Ignazio Stanganelli, and Fabio Falcini revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

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