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ORIGINAL ARTICLE

Patient presentation, skin biopsy utilization and cutaneous malignant melanoma incidence and mortality in northern Italy: Trends and correlations

Lauro Bucchi[1] | Silvia Mancini[1] | Federica Zamagni[1] | Emanuele Crocetti[1] | Luigino Dal Maso[2] | Stefano Ferretti[3] | Flavia Baldacchini[1] | Orietta Giuliani[1] | Alessandra Ravaioli[1] | Rosa Vattiato[1] | Angelita Brustolin[4] | Giuseppa Candela[5] | Simona Carone[6] | Giuliano Carrozzi[7] | Rossella Cavallo[8] | Ylenia Maria Dinaro[9] | Margherita Ferrante[10] | Silvia Iacovacci[11] | Guido Mazzoleni[12] | Antonino Musolino[13,14] | Roberto Vito Rizzello[15] | Diego Serraino[2] | Annibale Biggeri[16] | Ignazio Stanganelli[17,18] | Fabio Falcini[1,19] | the AIRTUM Working Group

[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]UOSD Epidemiologia e Registro Tumori (Dip. di Prevenzione ASL VT) c/o Cittadella della Salute, Viterbo, Italy

[5]Trapani Cancer Registry, Dipartimento di Prevenzione della Salute, Servizio Sanitario Regionale Sicilia, Azienda Sanitaria Provinciale (ASP), Trapani, Italy

[6]Registro Tumori di Taranto, Unità Operativa Complessa di Statistica ed Epidemiologia, Azienda Sanitaria Locale, Taranto, Italy

[7]Modena Cancer Registry, Public Health Department, Local Health Authority, Modena, Italy

[8]Cancer Registry – ASL Salerno, Salerno, Italy

[9]Siracusa Cancer Registry, Health Unit of Siracusa, 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]South Tyrol Cancer Registry, Bolzano, Italy

[13]Department of Medicine and Surgery, University of Parma, Parma, Italy

[14]Medical Oncology Unit and Cancer Registry, University Hospital of Parma, Parma, Italy

[15]Trento Province Cancer Registry, Unit of Clinical Epidemiology, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy

[16]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy

[17]Skin Cancer Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Forlì, Italy

[18]Department of Dermatology, University of Parma, Parma, Italy

[19]Local Health Authority, Cancer Prevention Unit, Forlì, Italy

Correspondence
Silvia Mancini, Romagna Cancer Registry, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Forlì, Italy.
Email: silvia.mancini@irst.emr.it

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Abstract

Background: The global increase in incidence of cutaneous malignant melanoma (CMM) occurring in the past decades has been partly attributed to increased diagnostic scrutiny of early lesions, with a potential phenomenon of overdiagnosis.

Angelita Brustolin died on 20 August 2022.

The reported positive linear relation between skin biopsy rate and incidence of early CMM is compatible with this hypothesis.

Objectives: We explored the ecological association between the trends in annual dermatologic office visit rates, skin biopsy rates, incidence rates of in situ and invasive CMM by tumour thickness category, and CMM mortality rates in the Emilia-Romagna Region (northern Italy).

Methods: Four cancer registries covering a population of 2,696,000 provided CMM incidence data for the years 2003–2017. Dermatologic office visit rates and skin biopsy rates were calculated using the Regional outpatient care database. All rates were age-standardized. Trends were described with the estimated average annual per cent change (EAAPC). Correlations were tested with the Spearman correlation coefficient.

Results: Incidence increased significantly. The increase was steeper for in situ CMM (EAAPC: men, 10.2; women, 6.9) followed by CMM <0.8 mm thick (9.1; 5.2), but the rates grew significantly for most subgroups of CMMs ≥0.8 mm thick. Mortality decreased significantly among women (−2.3) and non-significantly among men. For dermatologic office visit rate and skin biopsy rate the EAAPC were, respectively, 1.7 and 1.8 for men and 1.2 and 0.9 for women. Annual dermatologic office visit rate correlated with skin biopsy rate in both sexes. However, the proportion of skin biopsies out of dermatologic office visits was constant across the years (range: men, 0.182–0.216; women, 0.157–0.191).

Conclusions: In Italy, the increasing CMM incidence trend is, at least in part, genuine. Overdiagnosis—if any—is due to an increased patient presentation at dermatologic offices and not to a lower dermatologic threshold to perform biopsy.

INTRODUCTION

Substantial changes in sunbathing habits with more intense ultraviolet radiation exposure of brief duration and without protection[1,2] and an increasing use of indoor tanning beds played a central role in the steep rise in incidence rates of cutaneous malignant melanoma (CMM) that has been reported in the last several decades from virtually all Caucasian populations studied.[3–10]

Most—but not all—of the incidence increase has been accounted for by early or thin CMM,[11–15] generally defined as having a thickness ≤1.00 mm,[11,14,15] and has been accompanied by a comparable upward trend for in situ CMM.[12,14,15] An intriguing hypothesis is that the progression of ultraviolet-associated CMM may be slower and its biological aggressiveness reduced. This would be supported by the positive association between the level of ultraviolet radiation exposure before diagnosis and the prognosis of the disease.[16,17]

However, the most agreed-upon interpretation of the different tumour-thickness-specific incidence trends is that they result from early detection practices. Firstly, the public awareness of the signs of the disease has grown, favouring skin self-surveillance and prompt presentation for nevus changes.[18] Secondly, there are data suggesting that large-scale diffusion of newer diagnostic technologies has led to an increased sensitivity of dermatologic screening at the population level[19–22] and to an associated phenomenon of overdiagnosis of biologically benign CMMs, that is, of cancers that would not progress over the patient's lifetime.[18,23] A systematic literature review and field studies have confirmed that the implementation of skin cancer screening interventions leads to an increase in the incidence of in situ and thin CMM.[24,25]

Other researchers have reported data at variance with the hypothesis of a key role of overdiagnosis in incidence trends. In the Netherlands, for example, the rates of both thin (≤1.0 mm) and thick (>4.0 mm) CMM have increased, accompanied by an increase in mortality too.[26] Only in recent years, a further steeper increase for in situ and thin lesions among men has suggested the coexistence of overdiagnosis with a true incidence increase.[23]

More emphasis on the contribution of overdiagnosis to the epidemiologic trend has been placed by those studies that have had access to skin biopsy data. Welch et al.[27] found a positive linear relation between the increasing incidence of CMM between 1986 and 2001 in the United States and a rise in skin biopsy rates. The increase was mostly in early-stage disease, and mortality remained stable. These observations have recently been updated to 2015 and substantially confirmed.[28] In a study of similar design, another research group from United States has obtained comparable results for in situ CMM whereas the association between skin biopsies and invasive CMM was less clear.[29]

In Italy, the incidence of CMM was first shown to be increasing by multicentre registry data collected since 1986.[30] We are conducting a nationwide multicentre cancer registry-based research project with the objective to update the descriptive epidemiology of the disease. In two previously published articles, we have shown that the upward incidence trend is still ongoing for both sexes (despite a risk decrease being observed in the most recent birth cohorts)[31] and that the rates of thin CMM are rising more steeply.[32] This has provided the rationale for a third round of analysis aimed at exploring the ecological association between the trends in annual dermatologic office visit rates, skin biopsy rates, incidence rates of in situ and early invasive CMM, and CMM mortality rates in a large administrative region of the north of the country over the last two decades. The results are reported herein.

METHODS

Source of data

Of the total 21 cancer registries participating in the project,[31] we took into consideration the six situated in the Emilia-Romagna Region (northern Italy) because the project coordinating centre had direct access to the local Regional outpatient care database (Italian: Assistenza Specialistica Ambulatoriale or ASA). The ASA database includes individual records of services delivered to non-admitted, non-emergency patients in outpatient clinics of the National Health Service. Four registries met the following eligibility criteria: (i) ≥10 consecutive years of registration, (ii) availability of mortality data for the registration period, (iii) availability of incidence data for in situ CMM, (iv) availability of tumour thickness information as a standard registration item, and (v) annual proportion of invasive CMM cases with missing tumour thickness information ≤25%. Their registration period was 2003–2017. Their registration area covered the provinces of Parma, Modena and Ferrara and the sub-region of Romagna. On 1 January 2010, the total resident population was 2,696,000.

Original data 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 (ICD-10), codes D03.0 to D03.9 for in situ CMM and C43.0 to C43.9 for invasive CMM.[33] Death for CMM were classified using both the International classification of diseases, 9th revision (ICD-9),[34] codes 172.0 to 172.9 and the ICD-10[33] codes C43.0 to C43.9.

The records of dermatologic office visits were extracted from the Regional ASA database using the codes of health services listed in Table S1. When a code was not specific to the dermatology discipline, the selection included the (Italian) term 'dermatologia', that is, 'dermatology'. Multiple skin biopsies from a single patient, performed during one or more dermatologic office visits, were included.

Case series

Table 1 gives the number of in situ and invasive CMM, the number of CMM deaths and the number of both types of dermatologic investigations available for analysis. The median patient age at diagnosis of in situ/invasive CMM was 64 years for men and 56 years for women. The number of

TABLE 1 Number of incident in situ and invasive CMM cases, CMM deaths, dermatologic office visits and skin biopsies, by sex. Emilia-Romagna Region (Italy), 2003–2017

	Men		Women		Total	
	No.	%	No.	%	No.	%
Cutaneous malignant melanoma cases						
In situ	1727	28.9	1726	30.3	3453	29.6
Invasive, by thickness						
<0.8 mm	2006	33.5	2129	37.4	4135	35.4
0.8–1.0 mm	427	7.1	429	7.5	856	7.3
>1.0–2.0 mm	586	9.8	551	9.7	1137	9.7
>2.0–4.0 mm	481	8.0	335	5.9	816	7.0
>4.0 mm	474	7.9	318	5.6	792	6.8
Unknown	281	4.7	209	3.7	490	4.2
Subtotal	4255	71.1	3971	69.7	8226	70.4
Total	5982	100.0	5697	100.0	11,679	100.0
Death	728		523		1251	
Dermatologic office visit	2,167,305		2,426,683		4,593,988	
Skin biopsy	428,436		420,907		849,343	

Abbreviation: CMM, cutaneous malignant melanoma.

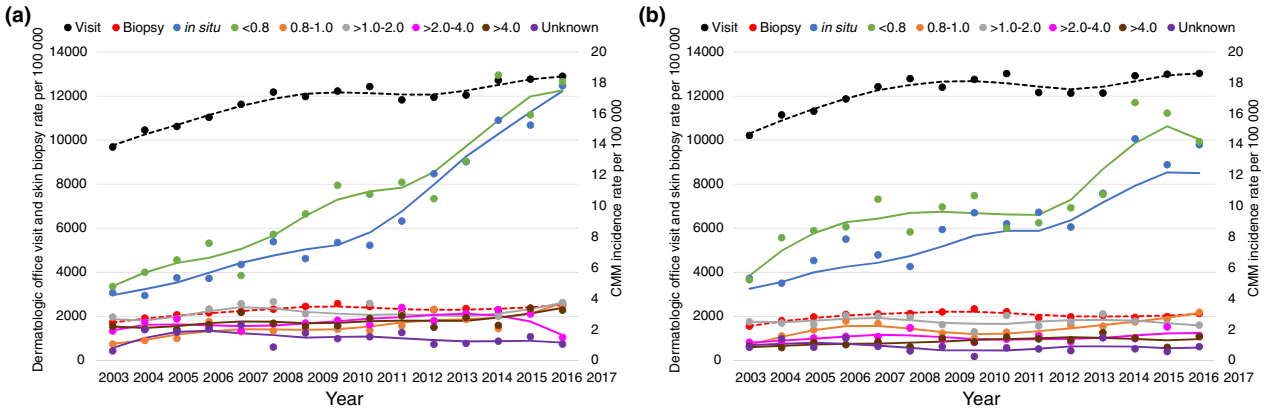

FIGURE 1 Curves of annual age-standardized (Europe 2013) incidence rates of in situ and invasive CMM by tumour thickness in millimetres, and annual dermatologic office visit rates and biopsy rates. A, men; b, women. A smooth fitted line was added to the observed values (points). Emilia-Romagna Region (Italy), 2003–2017.

invasive CMM cases which could be categorized by tumour thickness according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging criteria[35] (<0.8, 0.8–1.0, >1.0–2.0, >2.0–4.0 and >4.0 mm) was 7736 (94.0%). The median patient age at death was 71 for men and 74 for women. The dataset extracted from the Regional ASA database included 4,593,988 dermatologic office visits and 849,343 skin biopsies.

Statistical methods

The curves of annual age-standardized (Europe 2013) in situ and invasive CMM incidence rates, CMM mortality rates, dermatologic office visit rates and skin biopsy rates were plotted. A locally weighted regression (LOWESS) smoother was used to add a fitted curve to the observed values. Fifty per cent of the data, equivalent to a bandwidth of 0.5, were used in smoothing each point.

To assess the temporal trends in rates, the estimated average annual per cent change (EAAPC), with 95% confidence interval (CI), was calculated by fitting a generalized linear regression model for the natural logarithm of the age-standardized rate and year as a linear trend, with a Gaussian distribution and identity link function.

The Spearman's rank correlation coefficient (rho) was calculated to test the correlations between (i) dermatologic office visit rates and skin biopsy rates, and (ii) skin biopsy rates and incidence rates.

The annual proportion of skin biopsies out of dermatologic office visits and the annual proportion of total incident in situ/invasive CMMs out of skin biopsies, with exact binomial 95% CIs, were descriptively reported.

For literature comparison purposes, multivariable linear regression was used to evaluate the association between skin biopsy rates and incidence of CMM adjusted for year of diagnosis and age group. The model was used to estimate the number of additional melanomas stratified by sex that would be diagnosed per 1000 skin biopsies.

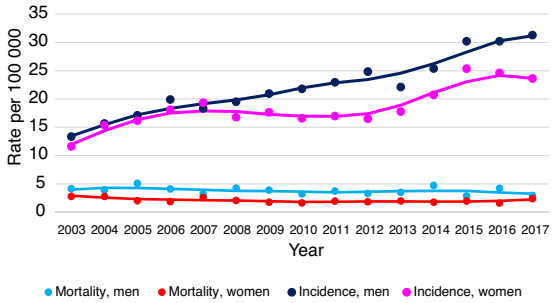

FIGURE 2 Curves of total annual age-standardized (Europe 2013) incidence rates of invasive CMM and annual age-standardized (Europe 2013) CMM mortality rates, by sex. A smooth fitted line was added to the observed values (points). Emilia-Romagna Region (Italy), 2003–2017.

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

RESULTS

Figure 1 shows the curves of annual incidence rates of in situ CMM and invasive CMM by tumour thickness, annual dermatologic office visit rates and annual biopsy rates. Among men (Figure 1a), an increasing trend was visually discernible for many subgroups of lesions and for both dermatologic investigations. The slope of the curve, however, was steeper for in situ and early invasive CMM. A comparable pattern was observed among women (Figure 1b).

Figure 2 shows the continuously-rising curves of total annual incidence rates of invasive CMM, by sex, as contrasted with annual CMM mortality rates. The latter appeared to be slightly decreasing in both sexes. The divergence between the two trends was more and more pronounced.

Table 2 shows the average annual ASR of all subgroups of lesions, of CMM deaths, and of dermatologic investigations and a statistical assessment of the above trends. In the male

TABLE 2 In situ and invasive CMM incidence, CMM mortality, dermatologic office visits and skin biopsies: Average annual age-standardized rates and trends, by sex. Emilia-Romagna Region (Italy), 2003–2017

	Men		Women	
	ASR (95% CI)	EAAPC (95% CI)	ASR (95% CI)	EAAPC (95% CI)
In situ	9.0 (8.6; 9.4)	10.2* (8.9; 11.5)	8.0 (7.7; 8.4)	6.9* (5.2; 8.5)
Invasive, by thickness				
<0.8 mm	10.3 (9.9; 10.8)	9.1* (7.4; 10.7)	10.2 (9.7; 10.6)	5.2* (3.1; 7.3)
0.8–1.0 mm	2.2 (2.0; 2.4)	4.9* (2.2; 7.5)	2.0 (1.8; 2.2)	2.3* (0.1; 4.5)
>1.0–2.0 mm	3.0 (2.8; 3.3)	0.7 (−1.5; 2.9)	2.5 (2.3; 2.8)	−0.2 (−1.7; 1.4)
>2.0–4.0 mm	2.5 (2.3; 2.8)	2.5* (0.4; 4.6)	1.5 (1.3; 1.7)	1.1 (−1.4; 3.6)
>4.0 mm	2.5 (2.3; 2.7)	2.3* (0.5; 4.1)	1.2 (1.1; 1.4)	3.7* (1.1; 6.3)
Unknown	1.5 (1.3; 1.7)	3.6 (−2.4; 9.7)	0.9 (0.8; 1.0)	4.5 (−8.6; 17.5)
Subtotal	22.1 (21.4; 22.8)	5.3* (4.4; 6.1)	18.3 (17.8; 18.9)	3.5* (2.1; 5.0)
Total	31.1 (30.3; 31.9)	6.7* (6.1; 7.3)	26.4 (25.7; 27.1)	4.5* (3.2; 5.8)
Mortality	3.9 (3.6; 4.1)	−1.4 (−3.3; 0.5)	2.1 (1.9; 2.3)	−2.3* (−4.1; −0.5)
Dermatologic office visit	11,755.5 (11739.7; 11771.3)	1.7* (1.2; 2.2)	12,206.4 (12190.7; 12222.2)	1.2* (0.6; 1.8)
Skin biopsy	2262.2 (2255.4; 2269.1)	1.8* (0.8; 2.8)	2031.4 (2025.1; 2037.7)	0.9 (−0.2; 2.1)

Abbreviations: ASR, age-standardized rate (European standard population 2013); CI, confidence interval; CMM, cutaneous malignant melanoma; EAAPC, estimated average annual per cent change.

Note: EAAPC is from a generalized linear model for the natural logarithm of the age-standardized incidence rate and year as a regressor.

*Significantly different from zero at the alpha level of 0.05.

population, the incidence was highest for invasive CMMs <0.8 mm thick followed by in situ CMMs. The rate of total invasive CMM, however, was almost 2.5-fold higher than that of in situ CMM. The biopsy rate was approximately 75-fold higher than that of total CMM. In the female population, most figures were lower but the pattern was virtually the same.

With respect to time trends, the two subgroups of earliest lesions were characterized by the largest EAAPC among men, but significant increases were observed for most subgroups of CMMs ≥0.8 mm thick. Mortality was confirmed to be slightly decreasing, and significantly so among women. The rate of increase of both dermatologic investigations was lower compared with those of in situ CMM and total invasive CMM. Among women, the EAAPCs followed the same pattern, although most trends were less rapidly increasing than among men and more often not statistically significant.

As shown in Figure 3, the annual dermatologic office visit rate correlated strongly and positively with skin biopsy rate in both sexes, although at a greater level of significance for men. In turn, the annual skin biopsy rate correlated positively with the annual incidence rate of in situ CMM (Figure 4) and early invasive CMM (Figure 5) among men.

Table 3 shows two consequences of the above trends. First, as a result of the close correlation between the annual dermatologic office visit rate and the annual skin biopsy rate, the proportion of skin biopsies out of visits was fairly constant across the years in both sexes, with a range of 0.182–0.216 for men and 0.157–0.191 for women; and second, since the rate of increase of dermatologic investigations was lower compared with those of in situ CMM and total invasive CMM, the proportion of the annual number of both groups of lesions combined out of the annual number of skin biopsies increased over time from approximately 0.010 to 0.020 for both men and women.

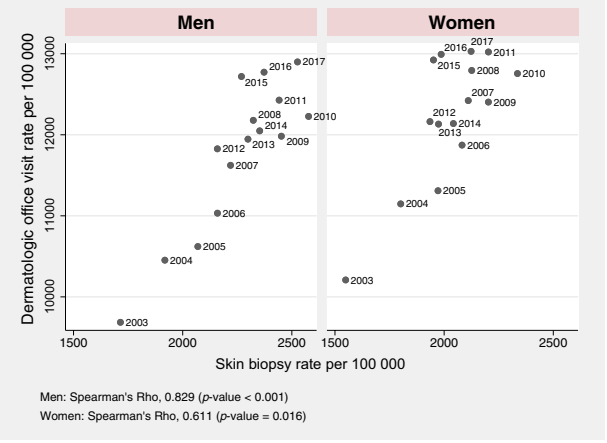

FIGURE 3 Scatterplot of annual age-standardized (Europe 2013) dermatologic office visit rates and skin biopsy rates, by sex. Emilia-Romagna Region (Italy), 2003–2017.

The additional number of in situ CMM per 1000 skin biopsies was 6.8 (95% CI: 4.2; 9.5) among men and 2.5 (95% CI: −0.1; 5.1) among women. The additional number of invasive CMMs per 1000 skin biopsies was 9.2 (95% CI: 6.2; 12.2) and 4.7 (95% CI: 0.6; 8.8), respectively.

DISCUSSION

Main findings

This study confirms previous Italian data indicating that the incidence increase observed in recent decades was steeper for, but not restricted to, in situ CMM and early invasive CMM.[32]

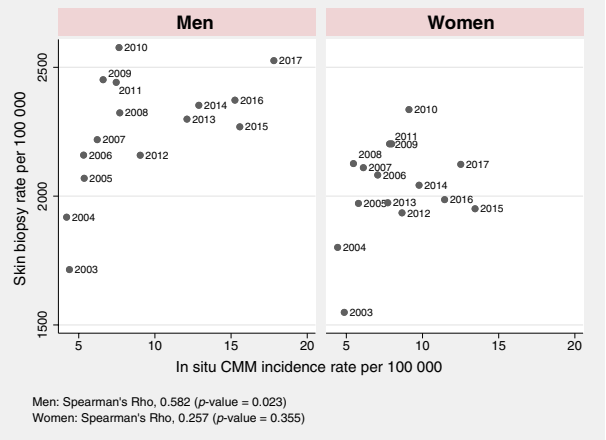

FIGURE 4 Scatterplot of annual age-standardized (Europe 2013) skin biopsy rates and in situ CMM incidence rates, by sex. Emilia-Romagna Region (Italy), 2003–2017.

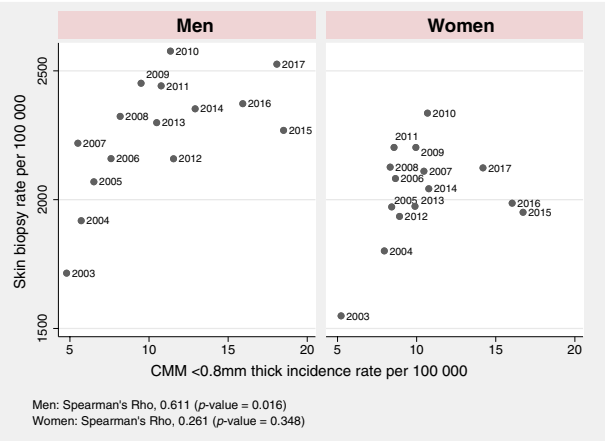

FIGURE 5 Scatterplot of annual age-standardized (Europe 2013) skin biopsy rates and CMM <0.8 mm thick incidence rates, by sex. Emilia-Romagna Region (Italy), 2003–2017.

Also, mortality rates were confirmed to have an opposite trend, although the decrease was significant only among women.

Our novel findings include the following: (i) in both sexes, the annual rate of dermatologic office visit correlated with the annual rate of skin biopsy; (ii) in turn, the annual rates of both dermatologic investigations correlated with the annual incidence rates of in situ CMM and early invasive CMM, even though only among men; (iii) however, the rate of increase of both dermatologic investigations was less than those of in situ CMM and early invasive CMM; (iv) the proportion of the number of skin biopsies out of the number of dermatologic office visits was fairly constant across the years; and (v) the annual proportion of incident in situ/invasive CMM cases out of skin biopsies rose with time.

Interpretation

The results of this and our previous studies[31,32] suggest that the increasing CMM incidence trend is, at least in part, genuine but do not allow to reject the hypothesis that it may be due, at least in part, to overdiagnosis. However, they indicate that overdiagnosis—if any—would depend on an increased patient presentation at dermatologic offices and not on a more liberal use of skin biopsy.

Welch et al. reported a positive linear relationship between the increasing incidence of CMM in the United States, mainly of early-stage CMM, and a concomitant increase in skin biopsy rate.[27,28] They interpreted the rise in CMM diagnoses to be primarily caused by a greater diagnostic scrutiny, that is, the combined effect of more skin examinations, lower clinical threshold to biopsy and lower pathologic threshold to report the morphologic changes as malignant. We can only partially confirm this scenario. In our data, there were more dermatologic office visits over time but the dermatologic threshold to biopsy, represented by the annual proportion of the number of skin biopsies out of the number of dermatologic office visits, was virtually constant at around 0.20 (a lower figure than the 0.31 observed in the Medicare data).[36] Rather, we observed a trend towards increasing specificity of the choice for biopsy, that is, an increasing proportion of histologic confirmation of CMM out of the annual number of skin biopsies (equivalent to an increasing predictive value for CMM).

These data are more consistent with the view that the rising incidence of CMM has promoted both patient self-referral and primary care physician referral for dermatologic screening.[18] Weinstock et al. have emphasized that the relationship between increased diagnostic scrutiny and CMM incidence could be a bidirectional one,[29] and that increased biopsies too may be driven, to some extent, by the underlying increase in disease rates. Our data are compatible with this hypothesis, but the increase in disease rate seems to have boosted patient presentation and not biopsy. Dermatologists, on the contrary, have approached the choice to biopsy with an increasing level of specificity, which is well explained by the diffusion of dermoscopy in Italy,[19–21] coupled with increasing prevalence of disease. It must be carefully considered that, to the authors' knowledge, the trends in patient presentation have never been evaluated in previous studies on the relationship between increased diagnostic scrutiny and the rising incidence of CMM.

Policy implications

So far, the strategies proposed to curtail the problem of overdiagnosis of CMM have all been centred on the work of dermatologists. Welch et al. have recommended to return to a 6-mm diameter threshold for the biopsy of pigmented skin lesions.[28] Others have argued that this approach would not be sufficiently safe, on account of the varying but not negligible prevalence of CMM of unpredictable clinical behaviour in series of pigmented skin lesions smaller than 6 mm,[37] 5 mm[38] and 4 mm.[39] An expectant management, with routine digital dermoscopy follow-up of high-risk individuals, might have a role in this setting[38] (incidentally, it has been proposed that, if the leading criterion regarding the diameter is no longer to detect CMM as early as possible but rather

TABLE 3 Number of incident in situ and invasive CMM cases, dermatologic office visits, and skin biopsies, and proportion of biopsies out of visits and of in situ/invasive CMM cases out of biopsies, by sex and calendar year. Emilia-Romagna Region (Italy), 2003–2017

Year	No. of dermatologic office visits	No. of biopsies	No. of in situ/invasive CMM cases	Proportion of biopsies out of visits (95% CI)	Proportion of in situ/invasive CMMs out of biopsies (95% CI)
Men					
2003	116,456	21,159	220	0.182 (0.179; 0.184)	0.010 (0.009; 0.012)
2004	127,675	24,138	252	0.189 (0.187; 0.191)	0.010 (0.009; 0.012)
2005	131,183	26,307	285	0.201 (0.198; 0.203)	0.011 (0.010; 0.012)
2006	137,466	27,628	327	0.201 (0.199; 0.203)	0.012 (0.011; 0.013)
2007	145,954	28,656	318	0.196 (0.194; 0.198)	0.011 (0.010; 0.012)
2008	154,504	30,317	357	0.196 (0.194; 0.198)	0.012 (0.011; 0.013)
2009	154,252	32,377	371	0.210 (0.208; 0.212)	0.011 (0.010; 0.013)
2010	159,627	34,557	402	0.216 (0.214; 0.219)	0.012 (0.011; 0.013)
2011	163,353	32,984	422	0.202 (0.200; 0.204)	0.013 (0.012; 0.014)
2012	156,208	29,342	469	0.188 (0.186; 0.190)	0.016 (0.015; 0.017)
2013	158,999	31,513	477	0.198 (0.196; 0.200)	0.015 (0.014; 0.017)
2014	162,606	32,761	549	0.201 (0.200; 0.203)	0.017 (0.015; 0.018)
2015	150,169	27,609	566	0.184 (0.182; 0.186)	0.021 (0.019; 0.022)
2016	123,435	23,656	463	0.192 (0.189; 0.194)	0.020 (0.018; 0.021)
2017	125,418	25,432	504	0.203 (0.201; 0.205)	0.020 (0.018; 0.022)
Women					
2003	132,859	20,846	235	0.157 (0.155; 0.159)	0.011 (0.010; 0.013)
2004	147,244	24,642	285	0.167 (0.165; 0.169)	0.012 (0.010; 0.013)
2005	150,678	27,178	316	0.180 (0.178; 0.182)	0.012 (0.010; 0.013)
2006	159,144	28,888	366	0.182 (0.180; 0.183)	0.013 (0.011; 0.014)
2007	168,097	29,536	372	0.176 (0.174; 0.178)	0.013 (0.011; 0.014)
2008	174,759	30,113	329	0.172 (0.171; 0.174)	0.011 (0.010; 0.012)
2009	171,662	31,801	388	0.185 (0.183; 0.187)	0.012 (0.011; 0.013)
2010	179,115	34,242	398	0.191 (0.189; 0.193)	0.012 (0.011; 0.013)
2011	184,502	32,651	393	0.177 (0.175; 0.179)	0.012 (0.011; 0.013)
2012	173,171	28,907	395	0.167 (0.165; 0.169)	0.014 (0.012; 0.015)
2013	174,079	29,718	404	0.171 (0.169; 0.172)	0.014 (0.012; 0.015)
2014	176,226	31,129	489	0.177 (0.175; 0.178)	0.016 (0.014; 0.017)
2015	163,820	26,081	520	0.159 (0.157; 0.161)	0.020 (0.018; 0.022)
2016	135,196	21,758	398	0.161 (0.159; 0.163)	0.018 (0.017; 0.020)
2017	136,131	23,417	409	0.172 (0.170; 0.174)	0.017 (0.016; 0.019)

Abbreviations: CMM, cutaneous malignant melanoma; CI, confidence interval.

to decrease the histologic evaluation of the smallest lesions, then the patients must be informed about this change in clinical strategy).[40] Other potential complementary approaches include quality assurance measures, in particular the establishment of well-defined diagnostic categories and of reliable criteria for their recognition, the regular participation in clinical/histological correlation review, the postponement of biopsy in the case of irritation and use of excisional rather than incisional biopsy.[18] More important, Italian data demonstrate that the large-scale use of dermoscopy improves the diagnostic accuracy both for CMM and benign lesions[19–21] and reduces unnecessary excisions.[22] Further diffusion of this technology should be favoured. In parallel, intensive research is critical to further improve the ability of dermoscopy to assist the dermatologists in determining, in vivo, which lesions are benign biologically.

It clearly appears from our data that patient referral practices from primary care, as well as self-referral, would need to be reconsidered. We propose this idea as a matter of debate and a recommendation for future research agendas.

LIMITATIONS

The ecological nature of this study tempers the strength of its conclusions. In addition, the availability and quality of the

data used need to be critically considered from two points of view. First, the relationship between increased diagnostic scrutiny and CMM incidence is likely to be multifactorial[41] and, in particular, to be modified by several unmeasured influences. For a more thorough analysis, we would need to take into account, for example, the extent of historical underdiagnosis of CMM,[42] the evolution of histologic criteria,[42] and the changed market forces in the healthcare system.[23]

Second, we encountered problems with the ASA skin biopsy codes, many of which are poorly specific for a suspicion of CMM. We decided to favour sensitivity over specificity by including all biopsy codes at least compatible with this indication. The same approach was used by Weinstock et al. who included any indication, skin cancer or not.[29] To compare their study with ours, we used multivariable linear regression and estimated the number of additional CMM cases per an additional 1000 skin biopsies. Our results (in situ CMM: men, 6.8; women, 2.5; invasive CMM: men, 9.2; women, 4.7) were of the same order of magnitude as those obtained by Weinstock et al. (in situ CMM: both sexes combined, 5.2; invasive CMM: both sexes combined, 8.1). All of these figures, however, were very low in absolute terms. A review of worldwide published data reported that as many as 12% biopsies of pigmented skin lesions are diagnosed as CMM.[43] This confirms that the analysis of administrative data has limitations and cannot be a substitute for classical clinical studies with primary data collection, although the use of linked administrative data enables to combine individual-level information from different sources and to answer questions requiring large sample sizes. A modelling approach, capable to integrate relevant data from separate population-based sources, may offer an alternative for future studies.

CONCLUSIONS

The results of this study leaves open the question of whether the increasing CMM incidence trend in Italy is influenced by overdiagnosis. However, they indicate that presumptive overdiagnosis—if any—would be caused by an increased patient presentation at dermatologic offices and not by a lower dermatologic threshold to perform biopsy. The dermatologists' decision to biopsy, on the contrary, appeared to be associated with an increasing level of specificity. The latter was mainly due to the diffusion of dermoscopy. We believe that the development of a strategy to counter the problem of overdiagnosis of CMM must be approached from a different perspective than is currently the case.

THE AIRTUM WORKING GROUP

The membership of the AIRTUM Working Group is as follows: Chiara Balducci (Romagna Cancer Registry, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) 'Dino Amadori', Meldola, Forlì); Francesca Bella (Siracusa Cancer Registry, Health Unit of Siracusa); Rossella Cavallo (Cancer Registry – ASL Salerno, Salerno); Claudia Cirilli (Modena Cancer Registry, Public Health Department, Local Health Authority, Modena); Simonetta Curatella (Latina Cancer Registry, Lazio); Stefano Ferretti (Romagna Cancer Registry, section of Ferrara, Local Health Authority and University of Ferrara, Ferrara); Rosario Tumino, Graziella Frasca, (Cancer Registry, Provincial Health Authority (ASP), Ragusa); Claudia Galluzzo (Registro tumori di Taranto, Unità operativa complessa di statistica ed epidemiologia, Azienda sanitaria locale Taranto); Fabrizio Stracci, Alessio Gili (Department of Medicine and Surgery, University of Perugia, Perugia); Antonella Ippolito (Integrated Cancer Registry of Catania-Messina-Enna, Azienda Ospedaliero-Universitaria Policlinico 'Rodolico-San Marco', Catania); Maria Michiara (Department of Medicine and Surgery, University of Parma; Medical Oncology Unit and Cancer Registry, University Hospital of Parma, Parma); Caterina Oriente (UOSD Epidemiologia e Registro Tumori (Dip. di Prevenzione ASL VT) c/o Cittadella della Salute, Viterbo); Silvano Piffer (Trento Province Cancer Registry, Unit of Clinical Epidemiology, Azienda Provinciale per i Servizi Sanitari (APSS) Trento); Tiziana Scuderi (Trapani Cancer Registry, Dipartimento di Prevenzione della Salute, Servizio Sanitario Regionale Sicilia, Azienda Sanitaria Provinciale (ASP), Trapani); Federica Toffolutti (Cancer Epidemiology Unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano); and Fabio Vittadello (South Tyrol Cancer Registry, Bolzano).

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AUTHOR CONTRIBUTIONS

LB conceptualized the study and drafted the initial manuscript. SM, FZ, FB, OG and AR analysed the data. RV, ABr, GCan, SC, GCar, RC, YMD, MF, SI, GM, AM, RVR and DS collected the data. EC, LDM, SF and IS critically reviewed the manuscript. ABi supervised the data analysis. FF supervised the data collection.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICAL APPROVAL

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

ORCID

Lauro Bucchi https://orcid.org/0000-0002-6771-8119
Silvia Mancini https://orcid.org/0000-0003-0673-3347

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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