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Unexpected reduction of mortality rates from melanoma in males living in central Italy

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Abstract

A registry-based study has been carried out in central Italy to investigate cutaneous melanoma incidence and mortality trends. The incidence of invasive (1492 cases analysed) and *in situ* (224 cases) cutaneous melanomas increased significantly from 1985 to 1997, in both genders. The increase of invasive tumours was mainly due to 'thin' ($\leqslant$1.00 mm) lesions, while thick ones showed stable rates. From 1985 to 1999, we evidenced a statistically significant decrease in mortality among males, the estimated annual percent change (EAPC) was −3.3%/year ($P <= 0.012$), but this was not observed among females (EAPC = 0.2, $P = 0.896$). The stage at diagnosis was worse for males than females at the beginning of the analysed period, therefore the former had more possibilities for improvement than females. This may partially explain this finding since mortality rates among females were also quite low during the late 1980s. However, the stable incidence rates of the thick forms of melanoma make this finding largely unexpected, and difficult to understand assuming that in the last decade no 'clear-cut' improvements in survival have been documented as a result of new treatments in advanced melanomas.

Keywords: Cancer registry; Cutaneous melanoma; Epidemiology; Incidence; Mortality; Population-based; Trend

1. Introduction

Very recently, different authors have pointed out some interesting changes in the epidemiology of melanoma. Mortality has stopped increasing after many decades of an upward trend [1] and a decreasing trend has already started to occur in many countries [2–5], although this is usually limited to females [2,4–7].

Moreover, this increase in incidence when analysed according to Clark's levels or Breslow's thickness categories is mainly due to the thin forms of melanoma [1,4,8–10].

Until now, little is known about such data in a Mediterranean population. Thus, we report data on the incidence and mortality trends of *in situ* and invasive cutaneous melanomas from central Italy.

2. Patients and methods

Data on incidence for the period of 1985–1997 were retrieved from the Tuscany Cancer Registry, a population-based cancer registry active (since 1985) in the provinces of Florence and Prato in central Italy.

The territory of the Tuscany Cancer Registry corresponds to two of the 10 provinces of the Tuscany Region. The registry covers an area with a population of 1 164 141 inhabitants according to the 1991 census (density 305 inhabitants per km^2). The territory is divided into 51 municipalities collected in three local health units. Approximately 1% of the residents in the area are foreign, 38% come from other European countries, 33% from Asia, 14% from Africa and 14% America.

The description of the criteria for collection, registration and analysis followed by the registry has been presented elsewhere [11]. Briefly, the registry receives clinical notes from all of the Italian public hospitals and from those among the private ones which are financed by the Regional Health Authority. When necessary,

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general practitioners (GPs) are also involved. Pathological reports are collected from all of the pathological departments that are active in the registry area and from the main ones of the Tuscany region. Death certificates of resident subjects are retrieved from the Regional Mortality Registry where all of the death certificates relative to residents in the Tuscany region are collected, checked, coded and stored. A recent estimate of Tuscany Cancer Registry (RTT) completeness was 97.4% for the whole case series [12].

The present analysis focused on cutaneous invasive melanomas; *in situ* melanomas were described separately.

Tumour microstaging was evaluated by means of both Clark's levels and Breslow's thickness, the latter grouped into two categories; 'thin' forms, with a favourable prognosis (1 mm or less) and 'thick' forms (more than 1 mm) [13].

Mortality data from the same area of the Tuscany Cancer Registry for the period of 1985–1999 were retrieved from the archive of the Regional Mortality Registry.

Incidence and mortality rates were analysed for the two age-groups, <60 and $\geqslant 60$ years. Rates were age-standardised on the European standard population using direct methods. The confidence intervals (CIs) of the age-standardised rates were calculated using the method developed by Fay and Feuer [14].

To analysed time trends, the estimated annual percent changes (EAPC) were computed. The EAPC are calculated by fitting a least squares regression line to the natural logarithm of the rates using the calendar year as a regressor variable. Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the regression parameter of the calendar year is equal to zero. The analysis was performed with the SEER*Stat software provided by the National Cancer Institute (http://seer.cancer.gov/seerstat).

To evaluate the strength of the relationship between the predictor (year) and the response (log of the rate), the squared Pearson's correlation coefficient (R^2) was computed. By definition, R^2 is the fraction of the total squared error that is explained by the model. Its value ranges from 0 to 100 as the fit of the model increases.

Relative survival—the ratio between the observed survival and the expected one on the basis of the mortality in the general population—was computed according to the method proposed by Hakulinen [15].[5] A Z-test was used to compare the survival curves of the two groups of cases up to a selected survival duration point.

3. Results

From 1985 to 1997, 1492 invasive cutaneous melanomas (670 males and 822 females) were diagnosed among the resident population. For 1392 cases (93.3%), histological verification was available.

The average age-adjusted incidence rate per year was 10.7 per 100 000 among males and 11.7 per 100 000 among females; the rates were 6.2 per 100 000 and 6.4 per 100 000 for males and females in 1985–1989 and 9.3 per 100 000 and 10.9 per 100 000 in 1993–1997, respectively (Table 1). Incidence increased significantly in both genders, (Fig. 1), EAPC $+5.5\%$/year (95% C.I. $+2.9$, $+8.2$; $R^2=0.63$) for males and $+6.7$ (95% C.I. $+4.0, +9.4$; $R^2=0.73$) for females (Table 1).

According to age, incidence increased both among subjects younger than 60 years (EAPC $=+6.5$, 95% C.I. $+3.6$, $+9.5$, $R^2=0.63$) and among older ones EAPC $=+5.2$ (95% C.I. $=+3.2, +7.1$, $R^2=0.75$).

Moreover, in the same time period, 224 *in situ* (Clark's level I) skin melanomas (95 in males and 129 in females) were also diagnosed (Table 1). The average standardised rate was 1.1 for males and 1.4 for females. The incidence of *in situ* lesions increased sharply and significantly over the time period both among males (EAPC $=+17.7$; 95% C.I. $+9.1$, $+26.9$, $R^2=0.43$) and females (EAPC $=+10.7$; 95% C.I. $+3.1$, $+18.9$, $R^2=0.35$) (Table 1).

There were 361 Clark II (24.2%), 414 Clark III (27.7%), 337 Clark IV (22.6%), 53 Clark V (3.6%)

Table 1
Cutaneous melanoma: number of invasive and *in situ* cases and deaths, and age-standardised (European population) incident and mortality) rates for 1985–1989 and 1993–1997 (or 1985–1999 for mortality) and corresponding Estimated Annual Percent Change (EAPC) for 1985–1997 (or 1985–1999 for mortality), for males and females

	Incidence														
	Invasive					*In situ*					Mortality				
	1985–1989		1993—1997			1985–1989		1993–1997			1985—1989		1995–1999		
	n	Rate	*n*	Rate	EAPC	*n*	Rate	*n*	Rate	EAPC	n	Rate	*n*	Rate	EAPC
Males	197	6.2	317	9.3	+5.5*	21	0.6	57	1.7	+17.7*	91	2.8	74	1.9	−3.3*
Females	242	6.4	415	10.9	+6.7*	32	0.8	78	2.3	+10.7*	68	1.6	86	1.6	+0.2
All	439	6.3	732	10.1	+6.1*	53	0.9	135	2.0	+13.9*	159	2.1	160	1.7	−2.0*

* $= P<0.05$.

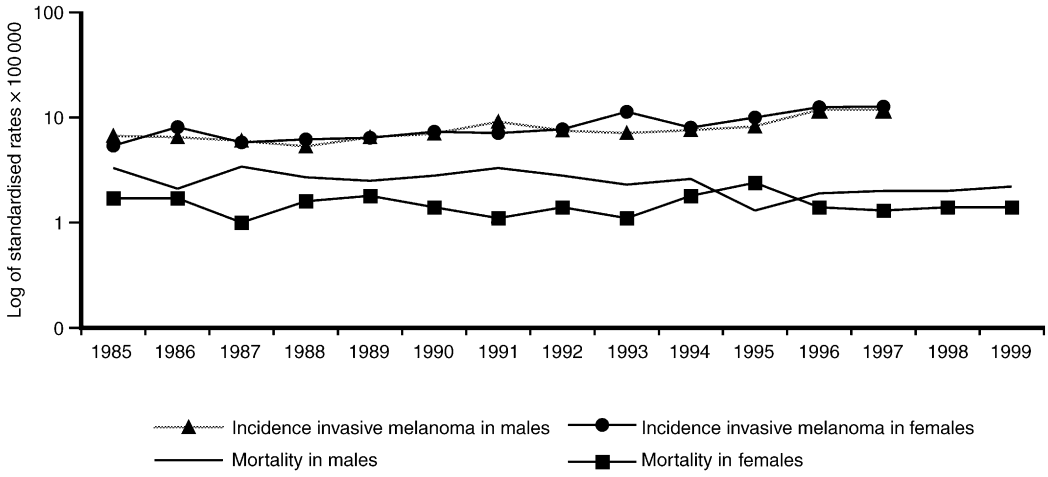

Fig. 1. Melanoma of the skin: incidence and mortality trends in central Italy, by gender.

cases, and 327 (21.9%) cases without Clark's definition. According to the Clark's levels, the most relevant increase in rates, for invasive lesions, was due to Clark's level II tumours EAPC = +14.3%/year (95% C.I. +11.2, +17.6; $R^2 = 0.91$). However, also level III showed a statistically significant increase EAPC = +6.2 (95% C.I. +2.3, +10.2; $R^2 = 0.57$). Rates were stable for level IV EAPC = +2.8 (95% C.I. −1.7, +7.5; $R^2 = 0.22$), for level V EAPC = +0.1 (95% C.I. −7.1, +7.8; $R^2 = 0.02$) and for those cases without Clark's definition, EAPC = +1.0% (95% C.I. −2.7, +4.9; $R^2 = 0.14$).

As regards Breslow's thicknesses, there were 507 cases (34.0%) with a Breslow's thickness ⩽1 mm, 590 (39.5%) >1 mm and 395 (26.5%) without a Breslow's definition. The standardised incidence rates for 'thin' (⩽1 mm) lesions increased significantly during the analysed period in both genders: EAPC = +16.1 (95% C.I. +11.4, +21.0; $R^2 = 0.86$) for males and EAPC = +14.6 (95% C.I. +10.0, +19.4; $R^2 = 0.77$) for females. In addition, 'thick' lesions (>1 mm) increased, but this was not statistically significant (EAPC = +1.3 among males $R^2 = 0.02$ and +3.7 among females $R^2 = 0.21$). Finally, rates were rather stable for tumours without a Breslow's thickness definition, EAPC = +0.3 (95% C.I. −3.1, +3.8; $R^2 = 0.01$).

In the same area, according to the Regional Mortality Registry, in the period of 1985–1999, there were 475 deceased subjects from skin melanoma; 260 (54.7%) males and 215 (45.3%) females. Standardised mortality rates during 1985—1989 were significantly higher among males (2.8 per 10^5; 95% C.I. 2.3–3.5) than females (1.6 per 10^5; 95% C.I. 1.2–2.1) and in 1995–1999, they became quite similar, 1.9 (95% C.I. 1.5–2.4) and 1.6 (95% C.I. 1.3–2.1), respectively (Table 1). As a consequence, we found that mortality showed a significant decreasing trend (Fig. 1), among males EAPC = −3.3 (95% C.I. −5.7, −0.9, $R^2 = 0.35$), but was stable EAPC = 0.2 (95% C.I. −2.7, +3.2 $R^2 = 0.01$) among females (Table 1).

According to age, mortality decreased significantly among subjects younger than 60 years (EAPC = −3.6, 95% C.I. −6.6, −0.6, $R^2 = 0.30$), but not among the older ones (EAPC = −0.6, 95% C.I. −2.6, +1.4, $R^2 = 0.03$).

As regards relative survival, 3-year rates for cases diagnosed in 1985–1987 were 65% for males and 86% for females ($z = 3.38$, $P = 0.0008$) and for those incident in 1995–1997, 84 and 92%, respectively ($z = 1.58$, $P = 0.562$).

4. Discussion

The present study from a southern European population showed, in agreement with recent data from populations of Northern Europe [5,6,9,10], that the epidemiology of melanoma has changed in the last decade. From the mid-1980s to to late 1990s, we evidenced an increasing incidence of malignant melanoma. This trend was mainly caused by the diagnosis of 'thin' lesions, i.e. Clark's levels II and III, and Breslow's thickness of ⩽1 mm, coupled with a relevant increase in the incidence of *in situ* lesions. These results are probably due to improvements in early detection but, surprisingly, no corresponding expected reduction in the incidence of thick tumours was observed. In contrast, the incidence of thick tumours showed stable trends or even a tendency to increase. Interestingly, we evidenced—in contrast with other published studies [2,4,6,7]—a significant decrease in mortality among males and stable rates among females.

All the relevant results (the increase in the invasive and *in situ* incidence rates, the increase in the incidence rates for thin lesions, stable rates for thick ones (at least for Clark IV, which corresponds to 86.4% of the thick

lesions), and decrease in male mortality) are based on models with a quite good 'goodness of fit'.

Since the late 1980s, a preventive campaign targeted at the general population has been active in the Florence area. This campaign involves the surveillance of pigmented skin lesions. An educational campaign was launched in 1989 and was repeated in 1992. It aimed to alert professionals (family doctors (GPs)) and the adult population living in the Florence area about the risks associated with 'changing' moles (conference and seminars for doctors, leaflets for the population). Facilities for rapid referral of subjects with self- or GP-detected suspicious lesions was given by means of a permanent Pigmented Lesion Clinic (PLC) working in the Dermatology Department of the University of Florence, the referral centre for the early diagnosis of melanoma in that area. Detailed data about the pattern of referral to the Florence PLC and tumour prevalence in the examined population have recently been reported.[16] As a partial explanation of the above-mentioned findings, we hypothesise that males—who had, at the beginning of the analysed period, 2-fold higher mortality rates than females—had benefited from an increased awareness about melanoma screening more than females. Indeed, males showed a clear reduction (that was more substantial then that in females) in the median value of Breslow's thickness (from 1.90 mm in 1985 to 0.83 mm in 1997 for males and from 1.35 mm to 0.83 mm for females). This may have influenced the overall gender-related prognosis that was different for cases diagnosed in 1985–1987, but become similar in 1995–1997. The fact that the reduction in mortality was found only in the young (less than 60 years) subjects is in agreement with the fact that younger age categories were more effectively targeted by the screening campaign than the older ones, the latter representing less than 10% of the population examined at the Florence PLC[16]. No inference about a different targeting of screening campaign according to gender can, however, be made, since there was an approximately equal distribution of sexes examined at PLC. This suggestion therefore needs to be addressed specifically by means of proper studies since it is more usual to observe the more active involvement of females than males in prevention programmes for melanoma [6].

According to changes in the incidence rates, it should be noted that the percentage of cases without a histology verification decreased in the RTT from 9.2% in 1985–1987 to 4.5% in 1995–1997. However, the incidence rate for these cases did not vary significantly over time (EAPC $= -3.7$, $P = 0.28$, $R^2 = 0.13$). Therefore, it seems unlikely that this had substantially influenced the changes in the rates for thin and thick tumours evidenced in this time period.

A crucial point remains to be explained, i.e. the mortality reduction in males in spite of stable (or even growing) incidence rates for thick tumours (Clark's IV-V/Breslow's thickness level >1 mm). Since no 'clear-cut' effects on overall survival have been reported for the adjuvant immunotherapy [17] and/or chemo-immunotherapy protocols adopted in the last decade in patients with advanced disease compared with those in use previously, it is difficult to explain the reasons for this unexpected—although promising—finding.

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