Cutaneous melanoma mortality starting to change: A study of trends in Northern Ireland

Anthony Montella[a], Anna Gavin[b], Richard Middleton[b], Philippe Autier[a], Mathieu Boniol[a,*]

[a]International Agency for Research on Cancer (IARC), BEC/BIO, 150 cours Albert Thomas, 69372 Lyon cedex 08, France
[b]Northern Ireland Cancer Registry (NICR), Queen's university Belfast, Grosvenor Road, BT126BJ Belfast, United Kingdom

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ABSTRACT

Incidence and mortality of melanoma have increased among men and women in Europe. We analysed the incidence and mortality of cutaneous melanoma (CM) in Northern Ireland. Three thousand eight hundred and thirty-seven incident cases of CM were reported to the Northern Ireland Cancer Registry (NICR) from 1984 to 2006 and 1177 melanoma deaths occurred from 1955 to 2007. Trends were analysed using joinpoint regression and a negative binomial model was fitted to test the linear trends for incidence adjusted for calendar year, age, sex and Breslow thickness. Age-adjusted incidence rates of CM increased significantly in both men and women (estimated annual percent change (EAPC): 4.8% and 2.5%, respectively). The increase was essentially due to thin melanoma (<1 mm). In contrast, there was a stabilisation of incidence of thick melanomas (⩾4 mm) in men and suggestion of a decrease in incidence of thick melanomas in women (EAPC: –1.5, 95% confidence interval (CI) –3.6;0.6). Mortality rates increased steadily in men over the whole period 1955–2004 (EAPC: 1.8%, 95% CI 1.1;2.5) whereas in women it increased until 1980 and decreased after (EAPC: –1.0%, 95% CI –2.5;0.6). We report for the first time a downward shift in all age mortality after steady increases but for women only. The plausibility of this shift is supported by similar downward trend in thick melanoma incidence in females only. Although there has been an active sun protection programme in Northern Ireland since 1990, the reason for the changes in female mortality which predates the programme remains to be fully understood.

1. Introduction

Incidence of cutaneous melanoma (CM) has increased worldwide over several decades.[1,2] Only Australia shows a declining incidence rate for young women and a stable rate for men.[3] Time trends analysis of melanoma incidence showed that the observed worldwide increase was essentially caused by increase in thin tumours with Breslow's thickness being less than 1 mm.[4–8]

Some authors described this change in Breslow's thickness in Europe by presenting the decrease in the proportion of thick melanomas and suggested that the global decrease in melanoma thickness could be the result of early diagnosis.[9] It has also been suggested that this early detection of melanoma has been the main factor in improving survival from melanoma.[10] However, some articles reported that the incidence of thick melanomas did not decrease in Europe,[4–6] and the observed decreasing proportions of thick melanoma could just be seen as an artefact due to the increase of thin melanomas.[11]

To better understand changes in the incidence of cutaneous melanoma, analysis must take into account, not only

information on the aggressiveness of tumours using Breslow's thickness but also importance should be given to the comparison between incidence and mortality statistics. The Northern Ireland Cancer Registry (NICR) has collected data on melanoma and Breslow thickness since 1984. Over the period 1993–2003, incidence rates of CM increased by 2.8% in men and not significantly by 1.1% in women.[12] In this paper, we analysed incidence trends of melanoma in Northern Ireland according to Breslow thickness, histological type and anatomical site for the period 1984–2006. We also analysed data on trends in CM mortality in comparison to the incidence trends.

2.   Materials and methods

Data collection on skin melanomas has occurred since 1984 in N. Ireland thanks to a specifically funded melanoma registry which was sub-sumed into the population based national cancer registry, the Northern Ireland Cancer Registry (NICR) on its establishment in 1993. The NICR covers a population of 1,740,000 inhabitants. Cancer registration in Northern Ireland is highly representative of the covered population with a completeness of 98.5% for melanoma[13] with a high rate of microscopic verification and a very low rate of death certificate only.[2]

Over the period 1984–2006, 3890 cases of CM were recorded. Melanomas occurring in the eye or genital organs were excluded from the dataset. Fifty-three cases of CM were excluded from the analysis because the age of the patient was not available. Analysis was therefore conducted on 3837 cases of CM (1446 males and 2391 females). Age was categorised into four groups (<35, 35–49, 50–74 and ⩾75 years old). Breslow thickness was reported in mm for about 85% of tumours. Anatomical site was coded using International Classifications of Diseases 10 (ICD10-4 digit) as follows: C430, C431, C432, C433 and C434 were located on 'Head and Neck', C435 corresponded to 'Trunk', C436 to 'Upper limb', C437 to 'Lower limb', C438 to 'Overlapping sites' and C439 to 'Unspecified site'. Histological types were defined according to the International Classifications of Diseases for Oncology (ICD-O 3rd edition) as follows: M87213 for 'Nodular Melanoma' (NM), M87423 for 'Lentigo Maligna Melanoma' (LMM), M87433 for 'Superficial Spreading Melanoma' (SMM), M87443 for 'Acral Lentiginous Melanoma' (ALM), M87203, M87303, M87403, M87723 and M87453 for 'Other and unspecified types'. However, analysis of incidence trends according to histological type was confined to 1984–1988; 1993–2003 and 2006 as for the periods 1989–1992 and 2004–2005 a high rate of missing values was reported (roughly 60%). This high rate of missing values was due to the way pathologists recorded the tumours in 1989–1992, and to electronic collection of reports at the Cancer Registry in 2004–2005. Processes of data collection were modified after these two periods. After exclusion of these periods, 21% of cases were classified as of 'other or unspecified type'.

Mortality data over the period 1955–2007 were extracted from the WHO mortality database and from national statistics using code '190' of ICD-7 for the period 1955–1967, code '172' from ICD-8 for the period 1968–1978, code '172' from ICD-9 for the period 1979–2000 and finally code 'C43' from ICD-10 for the period 2001–2007. Over the whole period,

1177 deaths from cutaneous melanoma were recorded (553 for males and 624 for females).

Incidence and mortality rates were standardised for age using Segi's world population[14] and expressed as new cases or deaths per 100,000 person-years (age standardised rate: ASRw). Overall linear trends in incidence and mortality over the whole period were summarised with the estimated annual percentage change (EAPC). We analysed in parallel incidence and mortality trend data, but as incidence was only available for a short period, and mortality data had on average only around 40 deaths per year, we did not consider the use of age-period-cohort modelling. The EAPC was calculated by fitting a linear regression to the natural logarithm of the incidence rates, using calendar year as a regression variable. The model was therefore $ln(rate) = a * x + b$, where x = calendar year. Then, $EAPC = 100 * (e^a - 1)$.

Joinpoint regressions were performed using the SEER program Joinpoint[15] to identify significant changes in incidence and mortality trend. Joinpoint regression is based on permutation tests[16] to identify an inflection point (hereafter called joinpoint) with a significant change in the slope of the trend. Parameters of the analysis were the following: a maximum of three joinpoints was allowed and a minimum of four points between two joinpoints was required. The delta method[17] was used to estimate the 95% confidence interval (CI) of the estimated ASRw from the model.

To test if the change in incidence was independent of other variables, we computed a negative binomial model of the incidence rate adjusting for the effects of calendar year, age, sex
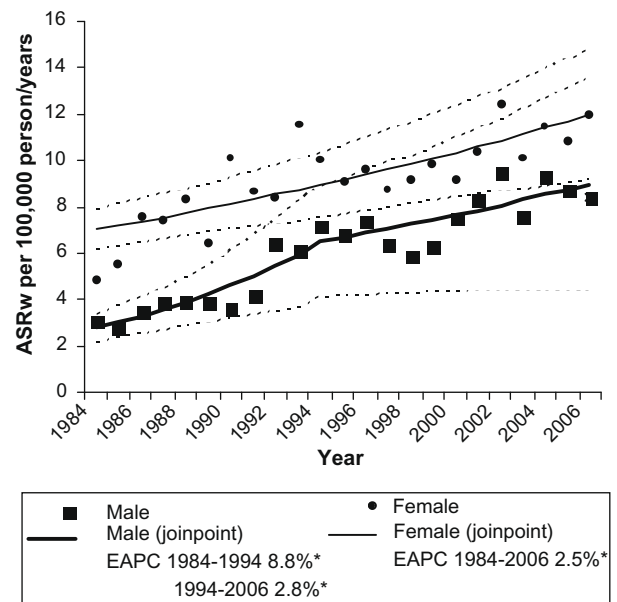
Fig. 1 – Evolution of the incidence of the cutaneous melanoma (CM) by gender in Northern Ireland for the period 1984–2006. *indicates significant trend. - - - each trend lines (plain line) is displayed between two hashed line corresponding to 95% confidence interval (CI) of the joinpoint regression. *Abbreviations*: ASRw, age standardised rate on the world standard population; EAPC, estimated annual percent change

and Breslow thickness. This model was preferred to a Poisson regression because initial analysis with a Poisson regression showed too much over-dispersion. Age was included in the model in four categories (<35, 35–49, 50–74, ≥75 years old) with 50–74 years as the reference group, sex in two categories using women as the reference, Breslow thickness in six categories (unknown, <0.5, 0.5–0.9, 1–1.9, 2–3.9, ≥4 mm) with <0.5 mm as the reference group, and year was entered in the model as a continuous term. Results of the model were expressed as percent change of the incidence rate to enable comparison with EAPC estimated with joinpoint regression. Coefficient could also be interpreted as relative risk by adding 1 to the percentage: a percent change of incidence of –23.8% being equivalent to a RR of 0.76. p-Values below 0.05 were considered as statistically significant.

3. Results

During the period 1984–2006, incidence of CM increased from 3.1 to 8.4 new cases per 100,000 person-years in men and from 4.9 to 12.0 per 100,000 person-years in women. However, changes in incidence did not evolve similarly for men and women (Fig. 1). In women, we found a continuous increase in incidence of 2.5% per year (95% CI 1.5;3.4) over the whole period. In men, incidence rate increased rapidly for the period 1984–1994 with 8.8% per year (95% CI 5.2;12.6), followed by a continuous increase similar to women of 2.7% (95% CI 0.9;4.7).

The increase in incidence of CM was essentially due to the continuous increase in melanomas thinner than 1 mm in both sexes with an EAPC of 7.5% for men and 4.0% for women (Figs. 2a and 3a). In contrast, there was a stabilisation of incidence of thick melanomas (≥4 mm) in men (EAPC: –0.2, 95%CI –2.1;1.9) and suggestion of a decrease in incidence of thick melanomas in women (EAPC:–1.5, 95%CI –3.6;0.6). There was no difference in incidence trends between melanomas thinner than 0.5 mm in and melanomas with a thickness between 0.5 and 1 mm (data not shown). In women with Breslow greater than 2 mm, we observed no increase in cutaneous melanoma incidence for ages younger or older than 50 years (Table 1).

Incidence rates of CM increased significantly in all age-groups for men and in all age-groups except 35–49 years in women (Figs. 2b and 3b).

Roughly 30% of melanoma occurred on the head and neck in men whereas more than 40% of melanoma occurred on the lower limb in women. Incidence rates of CM increased signif-
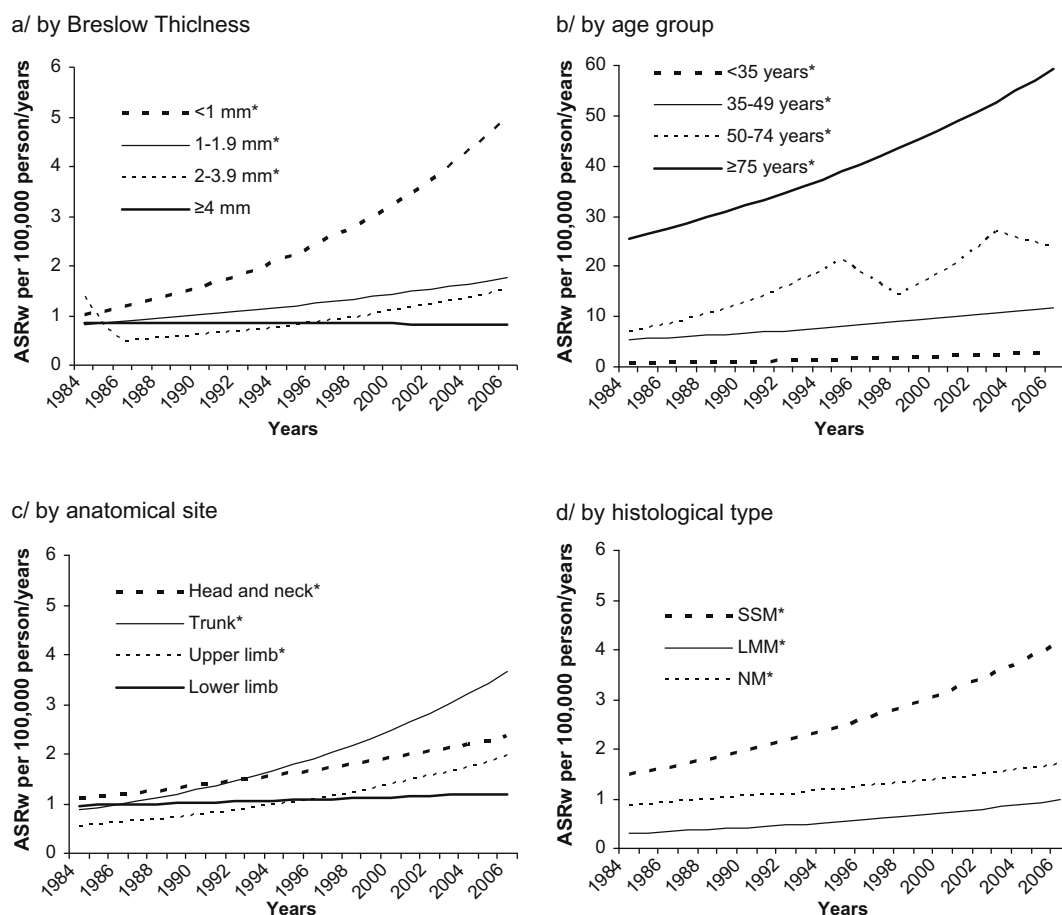

Fig. 2 – Evolution of the incidence among men in Northern Ireland for the period 1984–2006 according to co-variables. *Indicates significant increase or decrease of incidence rates without joinpoint over the period 1984–2006. *Abbreviations:* ASRw, age standardised rate on the world standard population, SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma and NM, nodular melanoma.
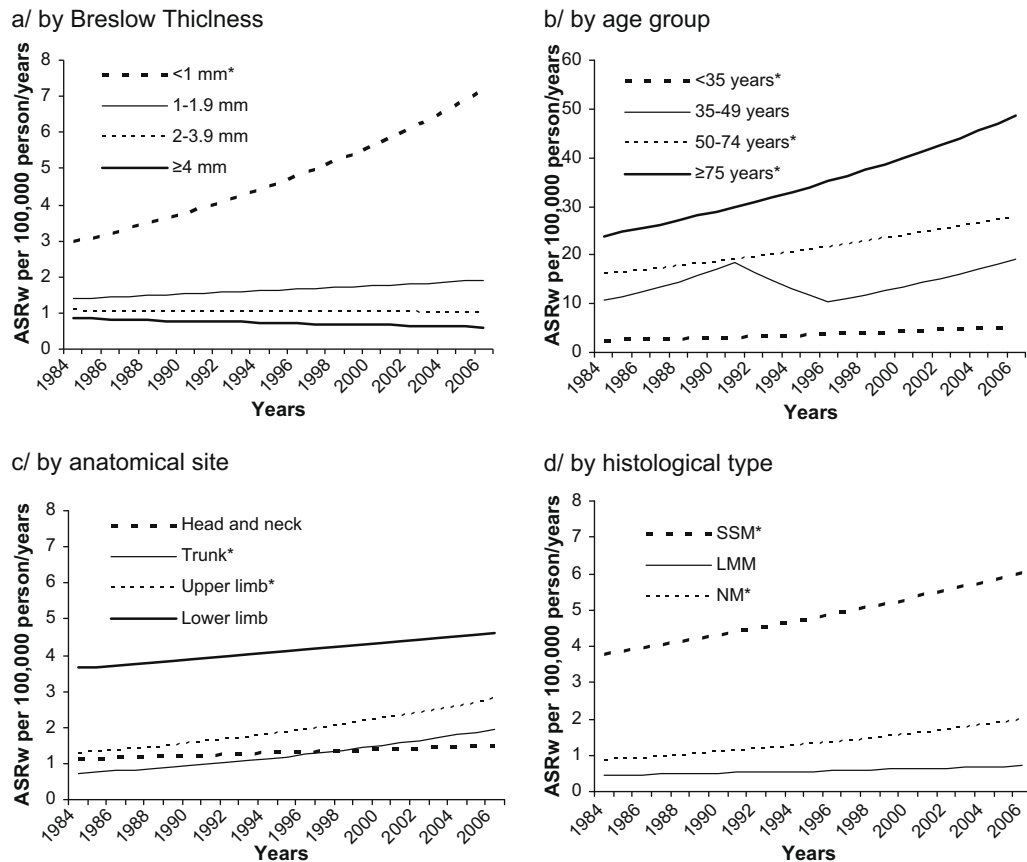
Fig. 3 – Evolution of the incidence among women in Northern Ireland for the period 1984–2006 according to co-variables. *Indicates significant increase or decrease of incidence rates without joinpoint over the period 1984–2006. *Abbreviations*: ASRw, age standardised rate on the world standard population; SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma.

icantly in all anatomical sites except for lower limb in men and for lower limb and head in women (Figs. 2c and 3c). Incidence rates of melanomas on the trunk and upper limb showed the highest increase in both sexes and more especially in patients younger than 50 years old.

Nodular melanoma and superficial spreading melanoma showed an increase of incidence in both sexes whereas lentigo maligna melanoma increased for men but not for women (Figs. 2d and 3d). Incidence rates of acral lentiginous melanoma did not increase over the period in either sex (data not shown).

Using negative binomial model with the aim of taking Breslow thickness into account, we found an overall increase in the incidence of 2.6% (95% CI 1.9;3.12) per year after adjusting by age and sex (Table 2). There was a good fit of the model to the data with a good correlation between predicted and observed values (Pearson r correlation $r = 0.66$). The increase in incidence remained stable after sensitivity analysis by changing categorical cut-points of co-variables. After checking any potential interaction between calendar period and other co-variables, only the interaction with Breslow thickness was significant ($p < 0.0001$). The increase in incidence according to Breslow thickness in the model with interaction gave an EAPC of 4.3% (95% CI 2.9;6.1) for incidence rates for melanomas thinner than 0.5 mm. For melanomas between 0.5 and 1 mm, EAPC

was 4.8% (95% CI 3.5;6.2). EAPC was 2.0% (95% CI 0.6;3.5) for melanomas between 1 and 2 mm and 1.3% (95% CI –0.2;2.9) for those between 2 and 4 mm. For melanomas thicker than 4 mm, we found an EAPC of –0.1% (95% CI –1.8;1.5).

Mortality rates increased from 0.1 to 1.7 per 100,000 person-years for men and from 0.6 to 1.8 per 100,000 person-years for women during the period 1955–2007 (Fig. 4). At the beginning of the period, the mortality rate for women was lower or equivalent with that for men. For the whole period, mortality rates increased continuously for men (EAPC 1955–2007: 1.8%, 95% CI 1.1;2.5) without any significant change in trends. Whereas in women mortality rates increased sharply until 1981 (EAPC 1955–1980: 5.2%, 95% CI 2.2;8.4) and decreased non-significantly afterwards (EAPC 1980–2007: –1.1%, 95% CI –2.5;0.6).

Restricting the mortality trend analysis to the period 1984–2006, corresponding to the period used for the incidence trend, did not modify the estimate of changes for men and women: for men the EAPC was 2.6% (95% CI 0.8;4.3) and it was –1.2% (95% CI –3.1;0.8) for women.

4. Discussion

Our study showed a continuous increase in the incidence of cutaneous melanomas for both sexes over the period 1984–

Table 1 – Evolution of the incidence of cutaneous melanoma (CM) in Northern Ireland for the period 1984–2006 according to Breslow thickness and age group.

Breslow thickness	Male			Female		
	N 1984–2006	EAPC (%) 1984–2006	ASRw 2006	N 1984–2006	EAPC (%) 1984–2006	ASRw 2006
Age <50 years old						
<1 mm	227	6.5[*]	2.3	558	3.4[*]	5.2
1–1.9 mm	96	3.4	0.6	158	1.4	2.2
⩾2 mm	89	0.5	0.5	93	–2.0	0.4
Age ⩾ 50 years old						
<1 mm	330	8.2[*]	13.9	535	5.2[*]	13.5
1–1.9 mm	164	3.5[*]	4.4	250	1.4	5.8
⩾2 mm	335	2.5[*]	9.6	445	–0.02	8.8

Abbreviations: ASRw, age standardised rate on the world standard population; EAPC, estimated annual percent change.
[*] Significance: *p*-value < 0.05.

2006 in Northern Ireland, this contrasts with a lower increase of mortality rates observed in the same period.

This increase in incidence of melanomas was essentially due to the increase of thin melanomas (<1 mm), mostly of superficial spreading melanoma type and occurring often on the trunk and upper limb. In 1984, the percentage of thin tumours was roughly 21% and the percentage of tumours occurring on the trunk was less than 9%. In 2006, thin tumours represented more than 50% of all tumours and the percentage of tumours occurring on the trunk was three times higher than in 1984. The increase observed for men older than 50 years was due to the increase in incidence of melanomas between 2 and 4 mm thick and not for melanomas greater than 4 mm thick.

A 'striking increase' in thin melanomas has been observed in many parts of Europe and in Australia.[3–8,18,19] The incidence of thick melanomas did not increase in either sex in France, Italy and Germany[4–6] but increased in Scotland for men[20] and in the Yorkshire area for older aged groups.[7] Considerable increases of incidence of melanomas occurring on the trunk and the upper limb were also reported.[21–23] Although legs were the commonest site in women, rates increased only slightly on this site.

The increase of incidence of CM observed in this study is not likely to be due to change in registration practice as registration methods for CM in Northern Ireland did not change over the study period and the number of Death certificate only cases for melanoma remained low for the whole period

Table 2 – Parameter values of the negative binomial model for incidence rate adjusted for the effects of calendar year, age, sex and Breslow thickness.

Parameter	N	Incidence change (%)[*]	95% CI lower (%)	Upper (%)
Calendar year	3837	2.6	1.9	3.2
<35 years	591	–80.8	–82.9	–78.5
35–49 years	813	–37.1	–43.3	–30.2
50–74 years ref.	1659	0		
⩾75 years	774	91.6	72.4	113.0
Male	1446	–23.8	–29.7	–17.4
Female ref.	2391	0		
<0.5 mm ref.	689	0		
0.5–0.9 mm	961	31.1	15.9	48.4
1–1.9 mm	668	–7.3	–18.7	5.7
2–3.9 mm	513	–21.8	–32.0	–10.1
⩾4 mm	449	–21.6	–32.3	–9.3
Unknown thickness	557	–13.8	–24.9	–1.2
Other negative binomial models for incidence rate with interaction between Breslow thickness and calendar year				
Calendar year	3837	4.3	2.9	6.1
<0.5 mm year ref.	689	0		
0.5–0.9 mm year	961	0.3	–1.7	2.3
1–1.9 mm year	668	–2.4	–4.3	–0.3
2–3.9 mm year	513	–3.0	–5.1	–0.9
⩾ 4 mm year	449	–4.4	–6.5	–2.3
Unknown thickness year	557	–2.8	–4.9	–0.6

Abbreviation: 95% CI, confidence interval.
[*] Coefficient could also be interpreted as relative risk by adding 1 to the percentage: a percent change of incidence of –23.8% being equivalent to a RR of 0.76.
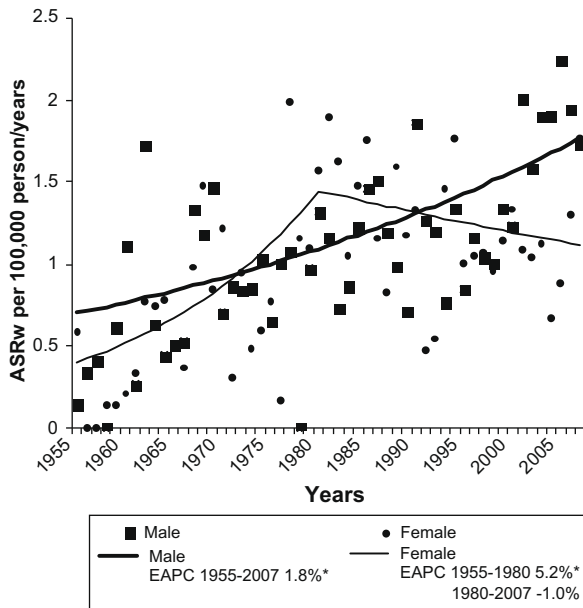
Fig. 4 – Evolution of the mortality by cutaneous melanoma (CM) by gender in Northern Ireland for the period 1955–2007 (WHO mortality database). *Indicates significant trend. *Abbreviations*: ASRw, age standardised rate on the world standard population; EAPC, estimated annual percent change.

(<0.01%). Moreover, if the completeness of the registry has improved during the period, we could have expected an increase of incidence of all types of CM.

It has been suggested that the increase of thin melanomas could reflect a change in classification of non-invasive melanomas into invasive melanomas[18] which could result in *in situ* melanoma being classified as invasive melanoma lower than 1 mm. However, this is unlikely since we observed no difference in the trends in melanomas thinner than 0.5 mm compared to those between 0.5 and 1 mm. Incidence of melanoma *in situ* was recorded by NICR and, as was observed in other registries,[24,25] it presents in Northern Ireland a stronger increase than that observed for invasive melanoma (data not shown).

A 'Care in the Sun' campaign against skin cancer began in 1989 in Northern Ireland with the aim to raise public awareness of the need to care in the sun and symptoms of melanoma.[26] Improved awareness of skin cancer could increase early detection of melanoma and especially of thin melanomas. Women are more susceptible to screening campaigns[27] and therefore we could expect an increase of thin melanomas in women. However, in our study, men showed the highest increase of thin melanomas, approximately roughly two times higher than that of women. Moreover, early diagnosis of thin tumours should be followed by an absolute decrease of thicker tumours. This was not observed in our study.

A recent study reported a significant decrease in melanoma mortality among women in Northern Ireland for the recent years.[28] However, this observation was difficult to interpret because results were not adjusted for multiple comparisons. In the present report, the plausibility of this shift is supported by similar downward trend in thick mela-

noma incidence in females only. Although there has been an active sun protection programme in Northern Ireland since 1990, the reason for the changes in female mortality which predates the programme remains to be understood. In the absence of new efficient treatment able to decrease mortality from advanced melanoma, discrepancies between incidence and mortality trends may also indicate changes in the nature of the disease. One hypothesis could be that, compared to men, greater proportions of women in Northern Ireland started working in cities after 1960,[29] which may have drastically changed chronic sun exposure among them. At the same time, recent trends in incidence may be more driven by intermittent exposures linked with greater access to holidays and increasing sunbed use, the latter being particularly fashionable among young women. These two hypotheses would suggest that melanoma associated with chronic or with intermittent sun exposure might have a different clinical course as the former would be more aggressive than the latter form of melanoma. This hypothesis is in line with recent suggestions that some melanomas are more associated with solar keratoses (mainly on the head and neck), that are associated with chronic sun exposure, while others are more associated with acquired nevi (mainly on the trunk and on limbs), that are more linked with intermittent sun exposure.[30]

In conclusion, in Northern Ireland, trends in melanoma mortality follow trends in incidence of thick melanomas, whereas an epidemic of small tumours is on-going, essentially of the SSM type that is not correlated with trends in mortality. The continuing increase of mortality rates among men from Northern Ireland supports the call that further prevention should target people having a low level of melanoma awareness such as older men.[26,31]

Conflict of interest statement

None declared.

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