Stage-specific incidence trends of melanoma in an English region, 1996–2015: longitudinal analyses of population-based data

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The aim of this study was to examine temporal trends in overall and stage-specific incidence of melanoma. Using population-based data on patients diagnosed with melanoma in East Anglia, England, 1996–2015, we estimated age-standardized time trends in annual incidence rates for each stage at diagnosis. Negative binomial regression was used to model trends over time adjusted for sex, age group and deprivation, and to subsequently examine variation in stage-specific trends by sex and age group. The age-standardized incidence increased from 14 to 29 cases/100 000 persons (i.e. 4% annually). Increasing incidence was apparent across all stages but was steepest for stage I [adjusted annual increase: 5%, 95% confidence interval (CI): 5–6%, and more gradual for stage II–IV disease (stage II: 3%, 95% CI: 2–4%; stage III/IV: 2%, 95% CI: 1–3%)]. Stage II–IV increase was apparent in men across age groups and in women aged 50 years or older. Increases in incidence were steeper in those aged 70 years or older, and in men. The findings suggest that both a genuine increase in the incidence of consequential illness and a degree of overdiagnosis may be responsible for the observed increasing incidence trends in melanoma in our population during the study period. They also suggest the potentially lower effectiveness of public health awareness campaigns in men and older people. ***Melanoma Res*** **00:000–000 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

The incidence of melanoma has increased dramatically in countries with predominantly White populations in recent decades and is projected to continue to increase for several countries [1–4].

Two key potential drivers of increasing incidence are increased population exposure to ultraviolet radiation (the principal known environmental risk factor for melanoma) [5], and overdiagnosis of tumours that would not spread during that patient's lifetime [6,7]. The former hypothesis (actual increase in the incidence of consequential illness) concords with increasing recreational exposure to sunlight since the 1950s [8,9]. However, stable trends in melanoma mortality despite increasing incidence have been observed, which may reflect either earlier diagnosis and more effective treatment of increasing consequential illness, or increasing overdiagnosis of relatively indolent lesions [10–14].

Analyses of stage-specific time trends of melanoma incidence could help to provide insights into mechanisms underlying increasing incidence: genuine increases in ultraviolet radiation exposure could be assumed to result in increased incidence of each stage equally, while overdiagnosis may lead to a disproportionately greater increase in early stage disease. Levell *et al.* [13] reported increasing incidence trends for stage I–III melanoma in 1991–2004, with a steeper increase for stage I disease. However, it is important to examine more recent patient cohorts, and potential differences in stage-specific variation over time by the sociodemographic group [15].

Patients and methods

Data

We analysed anonymized data on cases of primary invasive malignant melanoma (International Classification of Diseases for Oncology-3 code C43) diagnosed during

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1996–2015 in East Anglia, UK, for patients aged 15 years and older. These data were collected initially by the population-based cancer registry for the Anglia subregion of the East of England, and successor organizations who took over responsibility (currently the Public Health England National Cancer Registration and Analysis Service).

Patients who were first diagnosed with melanoma in the 15 years before the study period (1981–1995) ($n = 309/10\,199$) were a priori excluded from analyses, while for those with multiple tumours diagnosed during the study period (1996–2015), the earliest diagnosis was selected [16,17]. For patients with more than one tumour in a given year, the tumour with the more advanced stage at diagnosis was included.

Information was available on the year of diagnosis, stage at diagnosis, sex, age group (15–49 years and 5-year age groups thereafter), deprivation group, the method of diagnosis (e.g. histological or other basis) and survival status to death or censoring. Tumour stage was assigned by registry staff on the basis of clinical, imaging, and pathological information according to the 4th edition of the TNM classification (i.e. unified AJCC/UICC classifications) [18]. We combined stage III and IV cases into a single 'advanced stage' category, because of the small number of stage IV cases ($n = 155/9890$). The deprivation measure used was the Index of Multiple Deprivation (IMD) quintiles (fifths) of the income domain scores for the Lower Super Output Area of the patient's residence at diagnosis: IMD 2004 for diagnoses in 1996–2002; IMD 2007 for 2003–2006; IMD 2010 for 2007–2011; IMD 2015 for 2012–2015. As we used all available data for the period 1996–2015, a sample size calculation was not carried out.

Statistical analysis

Our general approach was to calculate incidence rates by treating the number of melanoma cases as the numerator and the estimated mid-year population residing within the boundaries of East Anglia as the denominator. Population estimates were stratified by the year of diagnosis, sex, age group and deprivation [19]. All analyses were performed in Stata v.13 (StataCorp., College Station, Texas, USA).

We first summarized the numbers of melanoma cases by sex, age group, deprivation, and stage, overall and by 5-year diagnosis periods. As 5.0% of patients (493/9890) had no recorded stage at diagnosis, we used multiple imputation before the main analyses – see below [20,21]. In a sensitivity analysis, we carried out a 'complete case analysis' (i.e. on those with nonmissing stage, $n = 9397$).

Incidence trends, by stage

We presented overall incidence trends and stage-specific incidence trends, by plotting sex-specific age-standardized rates (using the European Standard Population 2013) by year [22], for all cases and by stage at diagnosis. We plotted these trends on the log-scale, to allow a fair representation of relative changes over time among stage groups with different baseline incidence rates.

We initially considered the Poisson model for assessing temporal trends while adjusting for stage, sex, age group, deprivation and the interaction term stage × year, but variability in incidence rates was larger than assumed by the Poisson model ($P < 0.0001$). Hence, we adopted negative binomial models that include an additional parameter for variance overdispersion ('Model 1' in Box S1, Supplemental digital content 1, *http://links.lww.com/MR/A60*) [23].

Negative binomial models provided estimates of adjusted incidence rate ratios (IRRs). The IRR for the independent variable year (hereafter referred to as the 'annual IRR') represents the percentage increase in incidence per year as: $(\text{IRR} - 1) \times 100$ (e.g. an annual IRR of 1.05 is equivalent to a 5% increase per year).

Stage-specific incidence trends, by patient group

We explored whether stage-specific incidence trends varied by patient group, by investigating whether including three-way and four-way interaction terms between the two demographic variables (age and sex) and the stage × year interaction improved the fit of the original negative binomial model (which included main effects variables for stage, sex, age group, deprivation, year and the interaction stage × year). The investigation of interaction terms was performed using a step-wise process. We included interactions with demographic variables in descending order of the strength of association for the main effects in the original model and used the likelihood ratio test at each step to assess the improvement of fit by including the variable at that step.

The final model included the same main effect variables (i.e. stage, sex, age group, deprivation and year), as well as a four-way interaction term sex × age group × stage × year (and its two-way and three-way components; 'Model 2' in Box S1, Supplemental digital content 1, *http://links.lww.com/MR/A60*). As this updated model required a substantially greater number of degrees of freedom, these variables were more broadly categorized as two stage groups (I, II–IV); three age groups (15–49, 50–69 and ≥ 70 years); and three deprivation groups (least deprived, 2nd to 4th quintiles, most deprived). Finally, we calculated the adjusted annual IRRs for each patient group (all combinations of stage, sex and age group), predicted from this updated model.

Multiple imputation

We created five datasets (following the generic rule that the number of imputations should correspond to the percentage of missing data) [24], where missing stage was

imputed. We used multinomial logistic regression, on the basis of sex, age group, deprivation group, survival status, and the Nelson–Aalen estimator of the cumulative hazard [25], censoring survival information at 1 year post-diagnosis, to minimize bias from deaths unrelated to the melanoma. We carried out analyses as described above on each of these five datasets, using Rubin's rules to combine resulting estimates [26]. In sensitivity analysis, we carried out a 'complete case analysis' by restricting the analysis sample to only cases with observed stage, and compared the two approaches as the percentage change in the model coefficients (equivalent to the percentage change in IRRs on the log-scale).

Results

There were 9890 cases of melanoma diagnosed in East Anglia during 1996–2015 in an approximate population of 2.5 million during the study period. Table 1 shows the patients' characteristics by 5-year periods. Just over half (51%) of the cases were women, and just over half (53%) of the cases were under 65 years of age. Stage I disease accounted for the majority of cases (62%) during the entire study period. The proportion of younger patients (15–49 year-olds) decreased over time (from 31% in 1996–2000 to 20% in 2011–2015), while the proportion of stage I cases increased (from 57 to 64%).

Incidence trends, by stage

During the study period, the age-standardized incidence of melanoma increased substantially from 14.0 per 100 000 in 1996 to 29.4 in 2015 (i.e. by +4% annually) (Fig. 1 and Table S1, Supplemental digital content 1, *http://links.lww.com/MR/A60*). Overall (all-stage) incidence rates increased with time with a slight acceleration around 2005 (women: 15.0 per 100 000 in 1996 to 27.6, men: 13.3–32.5, Fig. 1). This overall time trend was mirrored by that for stage I cases, where the age-standardized incidence increased from 8.2 per 100 000 in 1996 to 20.3 in 2015 (+5% annually). Age-standardized incidence of stage II and stage III/IV cases also increased, but less steeply than for stage I cases (+2.8 and +1.9%, annually).

After adjustment for sex, age group and deprivation, there was strong statistical evidence for increasing incidence in stage I, II, and III/IV disease ($P < 0.0001$ for all adjusted annual IRRs), but a steeper increase for stage I disease [adjusted annual IRR for stage I disease: 1.05, i.e., a 5% increase per year, 95% confidence interval (CI): 1.05–1.06; stage II: 1.03, i.e., 3% increase per year, 95% CI: 1.02–1.04; stage III/IV: 1.02, i.e., 2% increase per year, 95% CI: 1.01–1.03; Table 2].

Stage-specific incidence trends, by sex–age subgroups

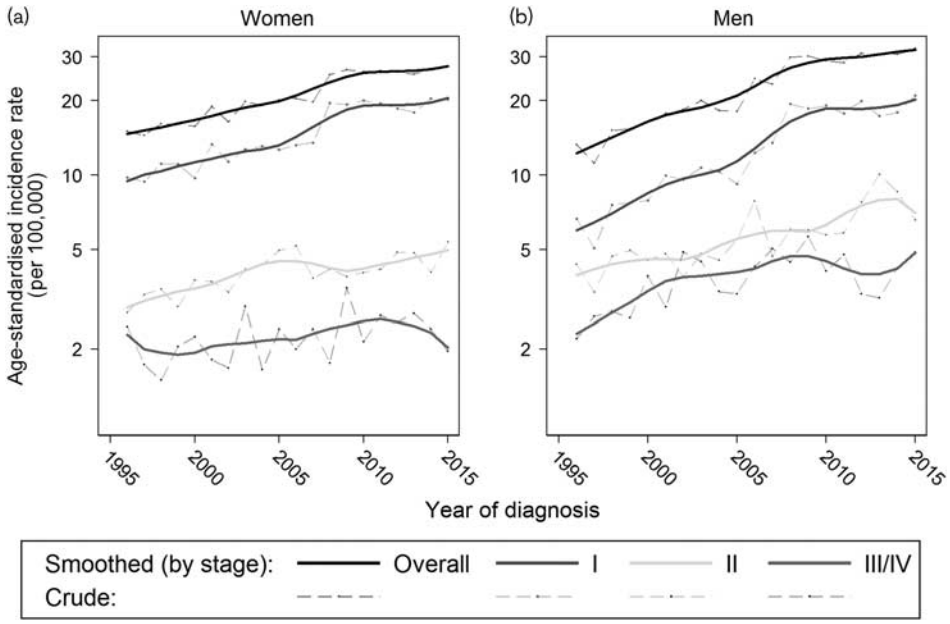
There was an increasing incidence of stage I disease for all age-sex strata, with adjusted annual IRR estimates significantly greater than 1 for all groups [lower bounds of 95% CIs for IRRs ranged from 1.01 to 1.10 (Fig. 2 and Table 3)]. Larger increases in the incidence of stage 1 disease over time were seen with increasing age [e.g. adjusted annual IRR for women, ≥70 years: 1.08 (95% CI: 1.08–1.09), women overall: 1.04 (95% CI: 1.04–1.05)]. Within each age group, adjusted annual IRRs were larger for men than women.

Table 1 Demographic and clinical characteristics of primary melanoma cases diagnosed in East Anglia during 1996–2015 (split into 5-year periods)

	1996–2000	2001–2005	2006–2010	2011–2015	1996–2015 (Total study period)
Total	1516 (100.0)	2033 (100.0)	2955 (100.0)	3386 (100.0)	9890 (100.0)
Sex					
Female	844 (55.7)	1095 (53.9)	1465 (49.6)	1675 (49.5)	5079 (51.4)
Male	672 (44.3)	938 (46.1)	1490 (50.4)	1711 (50.5)	4811 (48.6)
Age group (years)					
15–49	467 (30.8)	553 (27.2)	654 (22.1)	662 (19.6)	2336 (23.6)
50–54	172 (11.3)	175 (8.6)	210 (7.1)	253 (7.5)	810 (8.2)
55–59	150 (9.9)	229 (11.3)	278 (9.4)	264 (7.8)	921 (9.3)
60–64	148 (9.8)	198 (9.7)	391 (13.2)	366 (10.8)	1103 (11.2)
65–69	141 (9.3)	201 (9.9)	324 (11.0)	449 (13.3)	1115 (11.3)
70–74	152 (10.0)	209 (10.3)	353 (11.9)	396 (11.7)	1110 (11.2)
75–79	105 (6.9)	211 (10.4)	305 (10.3)	392 (11.6)	1013 (10.2)
80–84	100 (6.6)	142 (7.0)	233 (7.9)	298 (8.8)	773 (7.8)
>85	81 (5.3)	115 (5.7)	207 (7.0)	306 (9.0)	709 (7.2)
Deprivation (IMD quintile)					
1 (Least)	404 (26.6)	481 (23.7)	690 (23.4)	828 (24.5)	2403 (24.3)
2	406 (26.8)	608 (29.9)	880 (29.8)	1022 (30.2)	2916 (29.5)
3	383 (25.3)	532 (26.2)	865 (29.3)	921 (27.2)	2701 (27.3)
4	236 (15.6)	294 (14.5)	385 (13.0)	419 (12.4)	1334 (13.5)
5 (Most)	87 (5.7)	118 (5.8)	135 (4.6)	196 (5.8)	536 (5.4)
Stage at diagnosis					
I	863 (56.9)	1192 (58.6)	1935 (65.5)	2150 (63.5)	6140 (62.1)
II	349 (23.0)	449 (22.1)	572 (19.4)	652 (19.3)	2022 (20.4)
III–IV	210 (13.9)	287 (14.1)	382 (12.9)	356 (10.5)	1235 (12.5)
Missing	94 (6.2)	105 (5.2)	66 (2.2)	228 (6.7)	493 (5.0)

IMD, Index of Multiple Deprivation.

Fig. 1



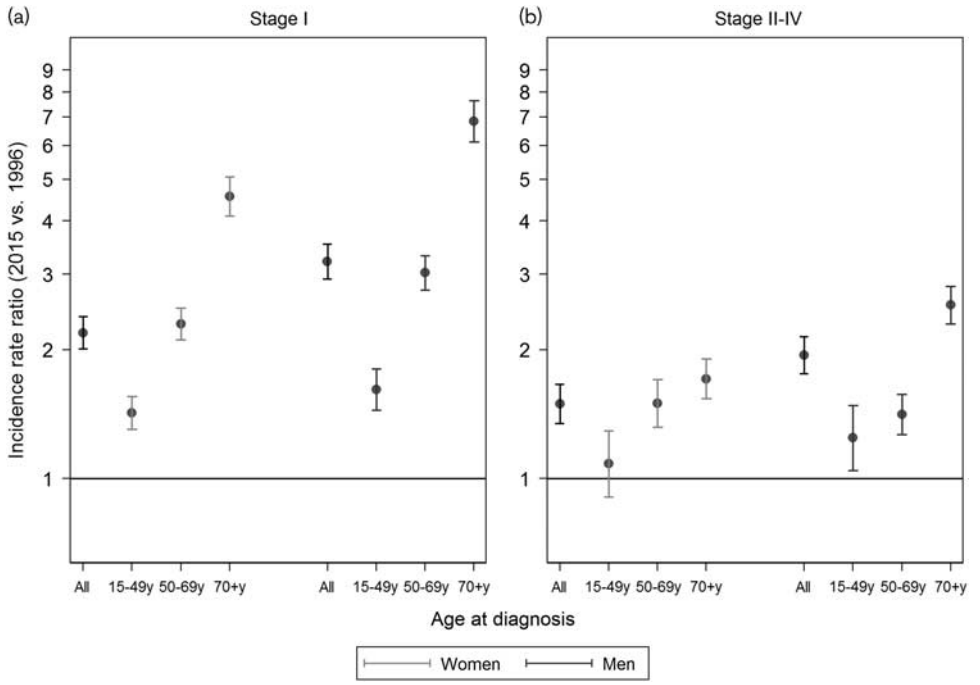
Age-standardized incidence of melanoma (smoothed and observed) by stage at diagnosis, for (a) women and (b) men. Smoothed rates are 'lowess' (locally weighted scatterplot smoothed) (i.e. the average of each observed yearly rate and rates in nearby years; in this case, the bandwidth was set at 0.2). For 493 patients (5% of the entire dataset) with missing values on stage, these values were imputed as described under 'Multiple imputation'.

Table 2 Adjusted incidence rate ratios of melanoma[a]

Variables	IRR	95% CI	*P* value[b]	% Change from IRR in complete-case analysis[c]	Increase in incidence per year[d] (%)	Increase in incidence across the study period 1996–2015[e] (%)
Sex (ref: female)						
Male	1.12	1.07–1.18	< 0.0001	6.8	–	–
Age group (ref: 65–59 years)						
15–49	0.22	0.20–0.24	< 0.0001	0.0	–	–
50–54	0.56	0.50–0.62	< 0.0001	−0.4	–	–
55–59	0.67	0.60–0.74	< 0.0001	0.4	–	–
60–64	0.82	0.74–0.91)	0.0001	2.5	–	–
65–69	–	–	–	–	–	–
70–74	1.18	1.07–1.31	0.0013	−2.3	–	–
75–79	1.36	1.23–1.51	< 0.001	11.1	–	–
80–84	1.45	1.30–1.62)	< 0.001	7.3	–	–
85+	1.55	1.39–1.74)	< 0.001	42.3	–	–
Deprivation (ref: least deprived)						
2	0.94	0.88–1.00	0.064	−21.3	–	–
3	0.84	0.78–0.90	< 0.0001	4.3	–	–
4	0.70	0.65–0.76	< 0.0001	−0.9	–	–
Most deprived	0.53	0.48–0.59	< 0.0001	−0.7	–	–
Stage at diagnosis (ref: I)						
II	0.44	0.39–0.50	< 0.0001	1.0	–	–
III and IV	0.30	0.26–0.35	< 0.0001	−3.6	–	–
Years of diagnosis (by stage at diagnosis)[f]						
Stage I	1.05	1.05–1.06	< 0.0001	1.2	5	153
Stage II	1.03	1.02–1.04	< 0.0001	−8.2	3	75
Stage III/IV	1.02	1.01–1.03	< 0.0001	5.4	2	46

AIC, Akaike Information Criterion; CI, confidence interval; IRR, incidence rate ratio; ref, reference category.
Pseudo-R^2 of Model 1 = 17%, AIC = 16 094.
[a]Estimated from negative binomial model including main effect variables for year, stage, sex, age group, deprivation and interaction stage × year. Exact model form provided as 'Model 1' in Box S1 (Supplemental digital content 1, *http://links.lww.com/MR/A60*). For 493 patients with missing values on stage (5% of entire dataset), these values were imputed as described under 'Multiple imputation'.
[b]Null hypothesis: IRR = 1. Presented up to 4 decimal points and up to two significant figures.
[c]On the log-scale (i.e. % change in β coefficients). Median change in model coefficients: 2.1%, interquartile range: −0.9 to 8.3%.
[d]Derived as: (IRR − 1) × 100.
[e]Derived as: (IRR^{19} − 1) × 100.
[f]Derived as: IRR = Exp[$\beta_{5\ year} + \beta_{6k}$(stage$_k$ × year)]; see Model 1 in Box S1 (Supplemental digital content 1, *http://links.lww.com/MR/A60*).

Fig. 2



Estimated incidence rate ratios (IRRs) of (a) stage 1 and (b) stages II–IV melanoma for 2015 (vs. 1996), according to sex and age groups. Displayed incidence rate ratios for stage-specific disease per year estimated from Model 2, to the power 19 (model form provided in Box S1; Supplemental digital content 1, *http://links.lww.com/MR/A60*). For 493 patients with missing values on stage, these values were imputed as described under 'Multiple imputation'.

Table 3 Adjusted incidence rate ratios of melanoma (both annual and across the entire period 1996–2015) for different patient subgroups[a]

	Stage I			Stages II–IV		
Age	Adjusted annual IRR (95% CI)	*P* value[b]	Adjusted IRR for entire period[c] (95% CI)	Adjusted annual IRR (95% CI)[c]	*P* value[d]	Adjusted IRR for entire period[c] (95% CI)
Women						
15–49	1.02 (1.01–1.02)	< 0.0001	1.42 (1.30–1.55)	1.00 (0.99–1.01)	0.38	1.08 (0.91–1.29)
50–69	1.04 (1.04–1.05)	< 0.0001	2.30 (2.11–2.50)	1.02 (1.01–1.03)	< 0.0001	1.50 (1.32–1.70)
≥ 70	1.08 (1.08–1.09)	< 0.0001	4.57 (4.11–5.07)	1.03 (1.02–1.03)	< 0.0001	1.71 (1.54–1.90)
Overall	1.04 (1.04–1.05)	< 0.0001	2.19 (2.01–2.39)	1.02 (1.02–1.03)	< 0.0001	1.50 (1.35–1.66)
Men						
15–49	1.03 (1.02–1.03)	< 0.0001	1.62 (1.45–1.81)	1.01 (1.00–1.02)	0.014	1.24 (1.04–1.48)
50–69	1.06 (1.05–1.07)	< 0.0001	3.02 (2.76–3.32)	1.02 (1.01–1.02)	< 0.0001	1.41 (1.27–1.58)
≥ 70	1.11 (1.10–1.11)	< 0.0001	6.84 (6.12–7.64)	1.05 (1.04–1.06)	< 0.0001	2.54 (2.30–2.82)
Overall	1.06 (1.06–1.07)	< 0.0001	3.21 (2.93–3.53)	1.04 (1.03–1.04)	< 0.0001	1.94 (1.76–2.15)

CI, confidence interval; IRR, incidence rate ratio.

[a]Sex-age-stage-specific IRRs were estimated from the updated negative binomial model, which included main effects year, stage, sex, age group, deprivation and four-way interaction sex × age group × stage × year. Exact model form provided as 'Model 2' in Box S1, (Supplemental digital content 1, *http://links.lww.com/MR/A60*). Overall IRRs were estimated according to Model 1 (form provided in Box S1, Supplemental digital content 1, *http://links.lww.com/MR/A60*). For 493 patients with missing values on stage (5% of the entire sample), these values were imputed as described under 'Multiple imputation'.

[b]Null hypothesis: IRR = 1. Presented up to 4 decimal points and up to two significant figures.

[c]Calculated as adjusted annual IRR to the power 19.

[d]Note that in 15–49-year-old men, the 95% CI of the adjusted annual IRR for stages II–IV contains 1.00 but the *P* value is 0.014, because of rounding to two decimal places.

Considering the respective adjusted annual IRRs for stage II–IV melanoma, increasing temporal trends in incidence were observed both in older women [e.g. IRR for ≥ 70 years: 1.03 (95% CI: 1.02–1.03)] and, more so, in older men [e.g. ≥ 70 years: 1.05 (95% CI: 1.04–1.06)] (Fig. 2 and Table 3). In younger people (age: 15–49 years) the increase in the incidence of stage II–IV melanoma was minimal, and not significant for women [adjusted annual IRR for women: 1.00 (95% CI: 0.99–1.01), $P = 0.38$; men: 1.01 (95% CI: 1.00–1.02), $P = 0.01$]. Increases in rates of stage II–IV disease were greater in older age, but this gradient was not as steep as that for stage I disease.

The complete-case sensitivity analyses produced similar results to those obtained in the main analyses, where missing stage was imputed (also see Table 2 and Fig. S1 and Table S2, Supplemental digital content 1, *http://links.lww.com/MR/A60*).

Discussion

Summary of main findings

The age-standardized incidence of melanoma increased substantially in the East Anglia region during 1996–2015. This increase predominantly reflected the increasing incidence of stage I cases, while the incidence of stage II–IV disease increased less steeply. In women aged under 50, though there was an increased incidence of stage I cases, this was not accompanied by an increase in the incidence of late-stage disease. For either sex, the increase in incidence was steeper in the oldest patients (≥70 years), and across age groups, increases in incidence were steeper in men than women.

Strengths and limitations

The principal strengths of this analysis are the use of population-based data covering an extensive period, using high quality and highly complete information on stage at diagnosis. To account for potential biases in estimates arising from missing stage data, we used multiple imputation. Nonetheless, as shown in sensitivity analyses, most estimates obtained from complete-case analysis were similar to those obtained using multiple imputed data.

The main limitation is that we cannot confidently infer the causes of the observed stage-specific incidence trends. Further analyses that consider changes in case-mix over time of other disease factors, for example, in tumour subsite (trunk, limbs, face, etc.) or diagnostic route (e.g. identification through healthcare encounters triggered by unrelated reasons), or in the rate of investigations for suspected melanoma in the general population, could help elucidate potential mechanisms. We examined data from the former East Anglia cancer registry, a geographically-defined population of South England whose residents are relatively older and more affluent, and more likely to be of White ethnic origin, compared with the rest of the English population [27]. These considerations might limit the generalizability of the findings, though not their internal validity. Analyses of England-wide data for the same 20-year era (to overcome these generalizability limitations) are not possible for our study period, because of the historically poor nationwide completeness of stage information for melanoma, until recent years. We examined the stratification of stage-specific incidence by sex and age group, but larger studies could additionally enable stratification by socioeconomic status.

Comparisons with the literature

Our study indicates a continuation (to 2015) of previously reported trends in our population (1991–2004) [13]. The observed steeper increase in stage I incidence mirrors upwards incidence rates of thin melanoma tumours (< 1.5 mm), and incidence rates of melanoma in certain subsites (e.g. trunk, head and neck) in studies covering similar time periods in Denmark [28,29], Finland [30], Scotland [31] and Northern England [32].

Implications for policy, practice and research

There are two main implications arising from the findings. First, the observed trends are compatible with a hypothesis of potential overdiagnosis of indolent cases, across age groups but it would be wrong to assign all of the increase in the incidence of melanoma to overdiagnosis. Had this been the case, no increase in advanced stage at diagnosis would have been observed in men (all age groups) and women (age ≥50 years). Second, the observed trends are also compatible with a hypothesis of increasing rates of genuinely consequential illness for older patients, particularly older men. Such a hypothesis is supported by evidence from South-Eastern Europe, where the increasing incidence of melanoma has been accompanied by increasing mortality for men and women aged 50 and older [33], and the USA, where increasing incidence was not accompanied by any decrease in tumour thickness for stage III and IV patients [34].

Quantifying the extent of overdiagnosis or increasing rates of consequential disease in a population is challenging. Nevertheless, our data suggest that both appear to be plausible, partial, explanations. These realizations emphasize the importance of shared decision making about investigating skin lesions and communication of issues around overdiagnosis in conversations with patients [35].

The 1–5% annual increase in advanced stage melanoma (II–IV) in women aged 50 and older and men in all age groups (Fig. 2 and Table 3), indicates a genuine increase in late-stage melanoma, which accounts for a 50% increase in incidence in older women and a 94% increase in older men over the 20-year study period (Table 3). This may reflect different risk behaviours with regard to sun exposure or different biological behaviours of melanoma in different age groups. The observation of different patterns in the incidence of stage II–IV melanoma women in the under 50s and those aged 50 and older warrants further investigation.

The increase in melanoma incidence puts pressure on limited health service budgets, particularly with regard to the use of novel, effective, but expensive biological treatments for late-stage disease, which have become available in recent years, offering life-extending management options. Our findings indicate an ongoing need for public health education campaigns, to increase

awareness of melanoma risk factors and symptoms and achieve earlier diagnosis, particularly in the elderly, and in men, who experienced the steepest increases in stage II–IV disease.

Conclusion

The findings suggest that both a genuine increase in the incidence of consequential illness and a degree of overdiagnosis are likely to be responsible for the observed increasing incidence trends in our population during the study period. They also suggest that targeting of men and older people in future public health awareness campaigns may be justified.

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Conflicts of interest

There are no conflicts of interest.

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