Papers

Skin biopsy rates and incidence of melanoma: population based ecological study

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Abstract

Objectives To describe changes in skin biopsy rates and to determine their relation with changes in the incidence of melanoma.

Design Population based ecological study.

Setting Nine geographical areas of the United States.

Participants Participants of the Surveillance Epidemiology and End Results (SEER) programme aged 65 and older.

Main outcome measures For the period 1986 to 2001, annual skin biopsy rates for each surveillance area from Medicare claims and incidence rates for melanoma for the same population.

Results Between 1986 and 2001 the average biopsy rate across the nine participating areas increased 2.5-fold among people aged 65 and older (2847 to 7222 per 100 000 population). Over the same period the average incidence of melanoma increased 2.4-fold (45 to 108 per 100 000 population). Assuming that the occurrence of true disease was constant, the extra number of melanoma cases that were diagnosed after carrying out 1000 additional biopsies was 12.6 (95% confidence interval 11.2 to 14.0). After controlling for a potential increase in the true occurrence of disease, 1000 additional biopsies were still associated with 6.9 (3.1 to 10.8) extra melanoma cases diagnosed. Stage specific analyses suggested that 1000 biopsies were associated with 4.4 (2.1 to 6.8) extra cases of in situ melanoma diagnosed and 2.3 (0.0 to 4.6) extra cases of local melanoma, but not with the incidence of advanced melanoma. Mortality from melanoma changed little during the period.

Conclusion The incidence of melanoma is associated with biopsy rates. That the extra cases diagnosed were confined to early stage cancer while mortality remained stable suggests overdiagnosis—the increased incidence being largely the result of increased diagnostic scrutiny and not an increase in the incidence of disease.

The incidence of melanoma of the skin is rising faster than any other major cancer in the United States. In 2002—the most recent year of data—the incidence was about six times that in 1950.

Some dermatologists suggest that this rising incidence may be more apparent than real[1–3] and acknowledge that diagnosis on the basis of histology is malleable; studies have shown that pathologists examining the same skin biopsy samples often disagree on the diagnosis of melanoma.[4–6] Dermatologists argue that some lesions that appear malignant to pathologists are biologically benign—an idea supported by data showing that most of the increased incidence is confined to early stage disease.[1 3 7] Finally, whenever physicians look more closely for melanoma, they find more cases.[7–10]

Population based data have not been reported on skin biopsies, the critical end point of surveillance. We examined data from Medicare, a nationwide health insurance for older Americans, to determine whether changes in the biopsy rate relate to the incidence of melanoma.

Methods

We used Medicare claims to obtain annual population based rates of skin biopsy for patients aged 65 and older in each of the nine geographical areas included in the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) programme from 1986 to 2001. We calculated the biopsy rates for each of 14 years (claims were unavailable for 1991 and 1992). To obtain the annual incidence of melanoma for the same population, we used the programme's statistical software (SEER*Stat, version 5.3.0).[11] We obtained stage specific incidence rates using the surveillance programme's four histological disease stages (in situ, local, regional, and distant) and summed them to produce an incidence rate for all stages combined. Using SEER*Stat's incidence based mortality method we also calculated melanoma incidence and disease specific mortality for all nine geographical areas combined.

Analysis

We used multiple linear regression to explore the relation between biopsy rate (independent variable) and melanoma rate (dependent variable). The unit of analysis was the surveillance programme's area in an individual year (nine areas, 14 years, 126 observations). To control for regional differences that may affect incidence (for example, latitude, racial composition, practice style) we included an indicator variable for area in all analyses. Our baseline analysis predicts the effect of 1000 additional biopsies on the number of melanoma diagnoses. The implicit assumption is that the true occurrence of disease may differ across areas but that it does not change over time. Our second analysis predicts the effect of biopsy assuming the true occurrence of disease has increased. To do this we used interaction terms for year and area, which allow the incidence of melanoma in each area to increase independently—that is, to have its own slope. Finally, we carried out four stage specific regressions using the same interaction terms when the dependent variable was the incidence of a specific disease stage. All

analyses were carried out using Stata 7.0 (see bmj.com for detailed model outputs).

Results

The incidence of melanoma in older people (≥ 65 years) in nine geographical areas of the US National Cancer Institute's Surveillance Epidemiology and End Results programme showed a steady, striking increase between 1986 and 2001 (fig 1). Most of the increase was in early stage disease (in situ and local) and not late stage disease (regional and distant). Mortality from melanoma changed little during the period.

Relation between biopsy and incidence

Between 1986 and 2001 the average biopsy rate across the nine areas increased 2.5-fold, from 2847 to 7222 per 100 000 population. Over this time the average incidence of melanoma increased 2.4-fold, from 45 to 108 per 100 000 population. Figure 2 shows the annual skin biopsy rate and incidence of melanoma for each area during the 14 years, illustrating a positive linear relation.

Table 1 provides estimates for the extra number of cases of melanoma diagnosed in association with an additional 1000 biopsies. Assuming no change in the true occurrence of disease, an additional 1000 biopsies resulted in 12.6 (95% confidence interval 11.2 to 14.0) number of cases of melanoma. Assuming the true occurrence of disease increased, 1000 additional biopsies were associated with an extra 6.9 (3.1 to 10.8) cases of melanoma. Stage specific analyses suggested that 1000 biopsies were associated with 4.4 (2.1 to 6.8) extra cases of in situ

Table 1 Estimate of extra cases of melanoma diagnosed per 1000 additional biopsies by stage of disease

Stage of disease	Assumption on incidence of disease	Extra cases diagnosed per 1000 biopsies (95% CI)	P value
All stages	No change	12.6 (11.2 to 14.0)	<0.001
All stages	Increase	6.9 (3.1 to 10.8)	<0.001
Stage specific:			
In situ	Increase	4.4 (2.1 to 6.8)	<0.001
Local	Increase	2.3 (0.0 to 4.6)	0.05
Regional	Increase	0.3 (−0.5 to 1.1)	0.45
Distant	Increase	−0.1 (−0.6 to 0.4)	0.68

melanoma and 2.3 (0.0 to 4.6) extra cases of local melanoma, but not with the incidence of advanced melanoma.

Discussion

Skin biopsy rates have increased substantially in each of the nine geographical areas participating in the US National Cancer Institute's Surveillance Epidemiology and End Results programme. This growth is associated with an increased rate of melanoma detection—a finding that persisted even after assuming an increase in the true occurrence of disease. From stage specific analyses we found that this relation was confined to local and in situ melanoma and was not evident in advanced disease. This finding supports the idea that the increased incidence of melanoma is largely the result of increased diagnostic scrutiny—that is, skin lesions are being biopsied that would not have been in the past.
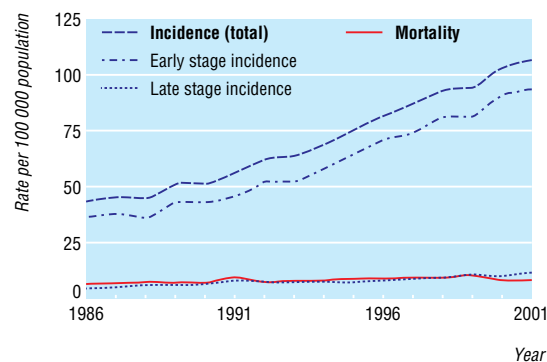

Fig 1   Incidence of melanoma and mortality in population aged 65 and older residing in one of nine US areas participating in Surveillance Epidemiology and End Results programme, 1986-2001. Early stage refers to in situ and local disease; late stage refers to regional and distant disease
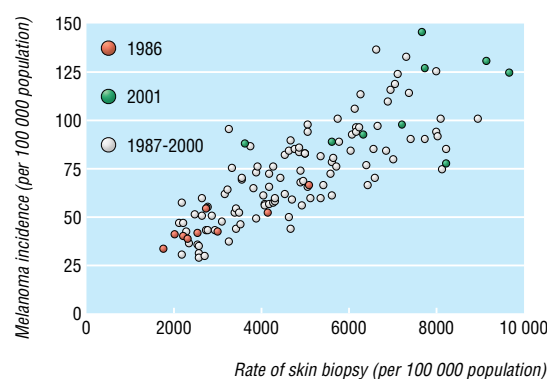

Fig 2   Scatterplot of annual rate of skin biopsy and incidence of melanoma for residents age 65 and older in each of nine US areas participating in Surveillance Epidemiology and End Results programme, 1986-2001

Table 2 Expected change in disease stage incidence and mortality given competing explanations for apparent rise in cancer incidence

Explanations for apparent rise in incidence	Expected change in incidence		Expected change in mortality
	Early stage disease	Late stage disease	
Increased diagnostic scrutiny, no change in true occurrence of disease	Increase	No change	No change
Increased true occurrence of disease	Increase	Increase	Increase

What is already known on this topic

Some dermatologists suspect that the rise in incidence of melanoma may reflect more skin biopsies, not more disease

What this study adds

The increasing incidence of melanoma between 1986 and 2001 in the United States is closely associated with biopsy rates

The increased incidence was mostly in early stage disease; yet mortality from melanoma remained stable

This pattern suggests overdiagnosis, largely as a result of increased diagnostic scrutiny and not an increase in the true occurrence of disease

Our data for trend also suggest that the true occurrence of melanoma has not changed. Table 2 outlines the expected change in stage specific incidence and mortality given different explanations for an apparent rise in incidence. The incidence of early stage disease has risen rapidly whereas the incidence for late stage disease and mortality have been relatively stable (fig 1), findings arguing against a dramatic increase in the true occurrence of disease. The predominant explanation for the apparent rise in melanoma incidence is instead overdiagnosis, the result of increased diagnostic scrutiny.

Some might posit an alternative explanation, arguing that stable mortality in the face of rising incidence reflects improved melanoma therapy. These improvements might be the net effect of two factors: starting treatment at earlier stages of disease, or better treatment for a given stage. But this seems implausible. For it to be true, the improvements afforded by early diagnosis and better treatment would need to exactly match the pace of the underlying increase in disease burden; they cannot be too slow or mortality would rise, nor can they be too fast or mortality would decrease.

The finding that the extent to which cancer is identified seems to be directly related to how closely it is looked for has been observed with several cancers, including lung cancer,[12] breast cancer,[13] renal cell carcinoma,[14] and neuroblastoma.[15 16] Perhaps the most powerful example is prostate cancer, where the number of cancers detected is directly related to how aggressively urologists biopsy the prostate. Historically, six needle biopsies were done but now many advocate 12 or more, noting that the more biopsy samples that are taken, the more likely cancer is to be found.[17–20] Some even advocate "saturation biopsy" (32-38 needle biopsies), as cancers can still be found microscopically in men who were cancer free on the basis of three or more prior biopsies.[21]

Our analysis has several limitations. Firstly, the data only represent people aged 65 and older. We do not know whether biopsy rates have changed in younger people or how any change might relate to the incidence of melanoma. Secondly, our biopsy rates include biopsies for lesions that were not considered to be related to melanoma before the biopsy, but rather basal or squamous cell carcinoma or a cutaneous manifestation of systemic disease. This concern is highlighted by biopsy rates that are nearly two orders of magnitude higher than melanoma incidence. Such imprecision in measuring exposure, however, only biases our results to the null.

Thirdly, some might question how we modelled an increase in the true occurrence of disease. Our analysis considers the independent effect of an area's biopsy rate on its melanoma rate if each area is allowed its own initial melanoma rate (an area specific y intercept) and its own melanoma growth rate (an area specific slope). By including a term for time to control for melanoma growth rate, we may have controlled for factors besides changes in true disease occurrence. Aspects of diagnostic scrutiny other than biopsy rate may also change over time, particularly the pro-

portion of biopsies carried out for pigmented lesions. Although we are unable to estimate precisely the true effect of biopsy rate, we were able to bound the estimate by carrying out analyses after assuming both increasing and stable true occurrence of disease (with and without time). Thus the true effect of 1000 additional biopsies is likely to be between 6.9 and 12.6 extra cases of melanoma diagnosed.

Finally, our investigation shares the limitation of all observational research in that although we show an association between biopsy rate and incidence, inferences about causation are more speculative. A causal relation is suggested, however, because the relation is confined to the category of disease (early stage melanoma) that would be expected to be related to diagnostic scrutiny. Furthermore, the finding of stable mortality in this population suggests that the bulk of these additional cases of melanoma may appear malignant on histology but are nonetheless biologically benign.

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