Analysis of the Melanoma Epidemic, Both Apparent and Real

Data From the 1973 Through 1994 Surveillance, Epidemiology, and End Results Program Registry

Leslie K. Dennis, PhD

Background: The incidence of melanoma has been increasing faster than that of any other cancer in the United States. It is unclear whether the increase is related to increased surveillance or other changes in the disease.

Objective: To examine changes in melanoma rates by several measures of severity of disease and to review the ways in which increased surveillance may cause lead-time bias through early detection or length bias through detection of clinically insignificant lesions as a basis for interpreting these changing rates.


Setting: United States Surveillance, Epidemiology, and End Results Program tumor registries.

Patients: A total of 47,638 cases of melanoma among white patients aged 20 years and older.

Main Outcome Measures: Relative incidence rates for melanoma by stage, and tumor thickness adjusted for age and sex.

Results: Localized-stage melanoma increased, but no significant change for distant-stage melanomas was seen. Among those diagnosed from 1988 through 1994, there were 22%, 26%, and 31% increases for tumor thickness less than 1.0 mm, between 1.0 and 3.0 mm, and 3.0 mm or greater, respectively. The 2-year mortality rates also increased over time.

Conclusions: While these data show large increases in early disease (localized stage, thin tumors), they also suggest some increase in advanced disease (thick tumors, 2-year mortality). This indicates that the increasing incidence rates of melanoma are not solely caused by increased early detection and diagnosis of clinically insignificant melanomas, but may also represent a true increase in cancer rates.

Arch Dermatol. 1999;135:275-280

The incidence of malignant melanoma of the skin is increasing faster than that of any other cancer in the United States.1 Melanoma incidence has increased from 5.7 cases per 100,000 in 1973 to 12.5 cases per 100,000 in 1994, while melanoma mortality has increased from 1.6 to 2.2 per 100,000 during the same period.2 It is estimated that 41,600 cases of melanoma in the United States will have been diagnosed in 1998 and 7,300 people will die of melanoma.3 There is debate as to whether this increase is the result of increased surveillance, a true change in the disease related to an increase in harmful exposures, or a combination of these factors.

Early detection of melanoma is an approach to control rates, since both melanoma incidence and mortality rates have been rising steadily during the 20th century.4 The American College of Preventive Medicine recommends screening for individuals at high risk of melanoma.5 Skin cancer screening can be conducted through self-examination or by a physician or can take place at a mass community screening.6 This kind of screening reflects increased surveillance of skin lesions.

There is debate over whether the increase in melanoma rates is real, because of early detection or detection of clinically insignificant melanomas.7-8 Increased surveillance can detect potentially deadly cancer earlier in its development (lead-time bias) but may also detect clinically insignificant tumors that may never progress to advanced disease (length bias). While incidence rates have sharply risen, it is argued that neither the death rate from melanoma nor the incidence of advanced-stage melanoma has decreased, implying that the increased incidence is not caused by the early detection of melanomas.7-12 Some researchers be-
METHODS

Incident cases of melanoma were obtained from 9 regions of the SEER of the National Cancer Institute, Bethesda, Md. Subjects were patients who had invasive malignant melanoma of the skin (International Classification of Diseases for Oncology topography codes C44.0 through C44.9 with behavior code 3) diagnosed from 1973 through 1994 and who were residents of populations served by SEER registries in the following areas: San Francisco–Oakland, Calif; Connecticut; Detroit, Mich; Hawaii; Iowa; New Mexico; Seattle–Puget Sound, Wash (1974-1994); Utah; and Atlanta, Ga (1975-1994). The primary sources of data were medical records from hospitals, with additional cases ascertained from pathologists, oncologists, and radiotherapists. Cases ascertained from autopsies only or death certificates only were excluded (n = 112). Analyses were limited to white patients in whom melanoma was diagnosed at age 20 years or older (n = 581 younger than 20 years). Population figures for 1973 through 1994 were developed by the Bureau of the Census under contract to SEER and were used in computing sex-specific and age-specific incidence rates. A total of 47,638 cases met the race and age criteria.

Incidence rates by sex, year, and severity of disease were computed as incident cases per 100,000 population. Rates were summarized across age groups for stability of rates to allow examination of severity of disease categories. Effect modification of incidence curves by sex was examined in the regression models by adding an interaction term and by comparison of sex-specific incidence curves. Severity of disease was examined through several measures, including stage, tumor thickness, the number of lymph nodes examined, the number of positive nodes, and Clark level of tumor thickness. Stage was defined as localized, regional, distant, or unstaged. Tumor thickness was measured in millimeters and grouped as less than 1.00 mm, 1.00 to 2.99 mm, and 3.00 mm or greater. Depth of penetration of the melanoma was also examined by means of Clark levels defined as levels 2 through 5, since level 1 is for in situ cases, which were excluded from all analyses. Tumors with an extension code that did not clearly fit into Clark levels 2 through 5, since level 1 is for in situ cases, which were excluded from all analyses. 13 Tumors with an extension code that did not clearly fit into Clark levels 1 through 5 were coded as “other.” While rates of melanoma were higher in men, the incidence curves were examined for changes over time. Death within 24 months of diagnosis was examined within the same periods as incidence. Since follow-up data were not available past December 31, 1994, incidence cases for 1993 and 1994 were excluded from the mortality analyses. The 2-year mortality rate was examined by diagnosis year of the cases. Data for all years were used to obtain the annual change in fatal incidence. For comparability, the RR reported for each period are for 5-year changes, since the most recent period contained only 5 years of information on 2-year mortality.

Incidence rates were adjusted for age and sex in the logistic model approximation to the Poisson regression model:

\[ \ln(\text{cases/population}) = \alpha + \beta_{\text{age}} + \delta_{\text{year}} + \gamma_{\text{sex}}. \]

Estimates of parameters in the model were computed by maximum likelihood techniques based on the log likelihood statistic. This yielded rate ratios describing the period effects on melanoma incidence for each year vs a reference year. For comparison of rates, 1988 was used as the reference category, since it was the first year available for most measures of severity of disease. The ratios were converted back to incidence rates to allow comparisons of incidence. To compute age-adjusted period-incidence curves, the rate ratios for each year vs the reference were multiplied by the observed incidence rates for the reference year.

Period trends of incidence by stage within 3 periods (1973-1979, 1980-1987, and 1988-1994) were analyzed with adjustment for age and sex (Table 1). For example, during the 1973 through 1979 period, a trend rate ratio (RR) was used to describe the log linear trend across the 7 years with the earliest year (1973) used as the reference group. In the log linear trend, \( e^d \) represents the ratio of rates for each subsequent year vs those diagnosed in the previous year, whereas \( e^w \) represents the ratio of rates that are 6 years apart (eg, 1979 to 1973). For each period, all years of data were used in the analyses; however, RR = \( e^w \), representing a 5-year period, was reported for comparability of varying lengths of periods and for comparability with trends in 2-year mortality rates. Confidence intervals were based on the trend RR and on its SE. \( P \) values reported were for tests of trend within each period.

Similar time trends were examined for tumor thickness, Clark levels, lymph nodes examined, and positive lymph nodes found. These trends compared rates from 1988 to 1994 (\( e^d \)).

The SEER publications report mortality data; however, such data are obtained from the National Center for Health Statistics but are not published with the SEER public access data. While annual mortality data are not available, the SEER public access data contain follow-up information on incident cases. As a surrogate for mortality, 2-year mortality by year of diagnosis (fetal incidence) was examined for changes over time. Death within 24 months of diagnosis was examined within the same periods as incidence. Since follow-up data were not available past December 31, 1994, incidence cases for 1993 and 1994 were excluded from the mortality analyses. The 2-year mortality rate was examined by diagnosis year of the cases. Data for all years were used to obtain the annual change in fatal incidence. For comparability, the RR reported for each period are for 5-year changes, since the most recent period contained only 5 years of information on 2-year mortality.

RESULTS

An average 3.6% increase in melanoma incidence per year was seen for 1974 through 1994. When time was divided into 3 periods, 1973 through 1979, 1980 through
1987, and 1988 through 1994, the largest increase from year to year was early, with annual increases of 6.6% (P < .001), 3.5% (P < .001), and 2.2% (P < .001), respectively. The additional increases between 1979 through 1980 and 1987 through 1988 can be seen in Figure 1. Only the 2.2% annual increase for 1988 through 1994 melanoma rates could be examined in greater detail by looking at tumor thickness, number of nodes examined, and number of positive lymph nodes reported.

Figure 1 shows the incidence of melanoma over time for localized stage by sex. A sharp increase in incidence for localized-stage melanoma was seen. Trends for localized-stage melanoma were identical through 1982 for both sexes, but diverged from 1983 through 1994 with higher rates for men. Figure 1 also shows the incidence of melanoma over time for regional, distant, and unstaged melanoma. While rates for men were higher than those for women (not shown), similar increases were seen for both sexes (parallel lines) and no effect modification by sex was found (P > .10). Therefore, rates for regional, distant, and unstaged melanomas were pooled for men and women to allow greater stability of these low rates. Table 1 describes the relative incidence rates of melanoma by stage during the 3 periods, 1973 through 1979, 1980 through 1987, and 1988 through 1994, adjusted for age and sex. The RR for localized-stage melanoma was significantly elevated in each time period, with the largest increase occurring in 1973 through 1979 (Table 1). Since effect modification was seen by sex for 1982 through 1994 localized disease, the rates were examined separately for 1980 through 1987 and 1988 through 1994. The sex-specific RRs for men and women, respectively, expressing a 4-year change as in Table 1 were 1.27 and 1.15 for 1980 through 1987, followed by 1.13 and 1.03 for 1988 through 1994. Regional-stage melanoma incidence was also seen to be increasing during 1973 through 1979. No trend in regional-stage melanomas was seen in 1980 through 1987 or 1988 through 1994. No trend was seen for distant-stage melanomas for any period.

Figure 2 shows melanoma incidence by the thickness of the tumor for 1988 through 1994. An annual increase of 3.3% was seen for small tumors less than 1.00 mm thick, a 3.9% increase for intermediate tumor thickness (1.00-2.99 mm), and a 4.6% increase in large tumors (3.00 mm or greater). A decrease over time was seen in missing information on tumor thickness (2.7% annual decrease). Table 2 compares changes in incidence rates by tumor thicknesses, showing the cumulative effect of the 3.3%, 3.9%, and 4.6% increase per year during the 1988 through 1994 period to be 22%, 26%,
and 31% increases for small, intermediate, and large tumors, respectively. These increases were even larger for patients aged 55 years and older, with 36%, 50%, and 35% increases, respectively. When thickness was divided into only 2 groups, similar trends were seen (no graph shown). This included an annual increase of 3.3% for tumors 1.50 mm or less and an increase of 4.4% for tumors greater than 1.50 mm (graphs not shown). Small and intermediate-size tumors had similar 2-year and 5-year survival rates. Two-year and 5-year survival rates were lower for large tumors (Table 2).

Incidence rates for 1988 through 1994 were also examined by Clark levels. An increase in incidence over time was seen for each level; however, the increase was only statistically significant for levels 2 and 4 and for missing data. An annual increase of 3.4% ($P < .001$) was seen for Clark level 2. Annual increases for levels 3, 4, 5, and “other” and for missing data were 0.7% ($P = .33$), 2.1% ($P = .01$), 1.5% ($P = .24$), 0.8% ($P = .44$), and 4.1% ($P = .004$), respectively. The percentage of melanomas where the lymph nodes were not examined increased from 86% in 1988 through 1989 to 90% for 1993 through 1994. Positive nodes were seen consistently over time in 2.9% of melanoma cases. However, a consistent percentage of cases with positive nodes does not necessarily mean that the rate of positive nodes in the population is not changing. Therefore, rates over time were examined. A 20% ($P < .001$) increase over 1988 through 1994 was seen in the rate of melanoma cases where no lymph nodes were examined. This may reflect an increase in early-stage disease. A 32% decrease in the rate of negative nodes was seen ($P < .001$), while a consistent rate over time was seen for 1 or more positive nodes found ($P = .94$).

Trends in 2-year mortality by year of melanoma diagnosis are reported by both death from melanoma or metastases and death from all causes (Figure 3 and Table 1). While 2-year survival increased and 2-year case-fatality decreased over time (data not shown), the 2-year mortality rates by year of diagnosis were seen to increase over time. Trends in 2-year mortality from all cancer deaths (International Classification of Diseases, Ninth Revision, codes of 140-239) were parallel to those for melanoma and metastases, with an annual average of 0.3 per 100 000 more deaths (not shown). For 1973 through 1979 was seen for each level; however, the increase was only statistically significant for levels 2 and 4 and for missing data. An annual increase of 3.4% ($P < .001$) was seen for Clark level 2. Annual increases for levels 3, 4, 5, and “other” and for missing data were 0.7% ($P = .33$), 2.1% ($P = .01$), 1.5% ($P = .24$), 0.8% ($P = .44$), and 4.1% ($P = .004$), respectively. The percentage of melanomas where the lymph nodes were not examined increased from 86% in 1988 through 1989 to 90% for 1993 through 1994. Positive nodes were seen consistently over time in 2.9% of melanoma cases. However, a consistent percentage of cases with positive nodes does not necessarily mean that the rate of positive nodes in the population is not changing. Therefore, rates over time were examined. A 20% ($P < .001$) increase over 1988 through 1994 was seen in the rate of melanoma cases where no lymph nodes were examined. This may reflect an increase in early-stage disease. A 32% decrease in the rate of negative nodes was seen ($P < .001$), while a consistent rate over time was seen for 1 or more positive nodes found ($P = .94$).

Trends in 2-year mortality by year of melanoma diagnosis are reported by both death from melanoma or metastases and death from all causes (Figure 3 and Table 1). While 2-year survival increased and 2-year case-fatality decreased over time (data not shown), the 2-year mortality rates by year of diagnosis were seen to increase over time. Trends in 2-year mortality from all cancer deaths (International Classification of Diseases, Ninth Revision, codes of 140-239) were parallel to those for melanoma and metastases, with an annual average of 0.3 per 100 000 more deaths (not shown). For 1973 through 1979 was seen for each level; however, the increase was only statistically significant for levels 2 and 4 and for missing data. An annual increase of 3.4% ($P < .001$) was seen for Clark level 2. Annual increases for levels 3, 4, 5, and “other” and for missing data were 0.7% ($P = .33$), 2.1% ($P = .01$), 1.5% ($P = .24$), 0.8% ($P = .44$), and 4.1% ($P = .004$), respectively. The percentage of melanomas where the lymph nodes were not examined increased from 86% in 1988 through 1989 to 90% for 1993 through 1994. Positive nodes were seen consistently over time in 2.9% of melanoma cases. However, a consistent percentage of cases with positive nodes does not necessarily mean that the rate of positive nodes in the population is not changing. Therefore, rates over time were examined. A 20% ($P < .001$) increase over 1988 through 1994 was seen in the rate of melanoma cases where no lymph nodes were examined. This may reflect an increase in early-stage disease. A 32% decrease in the rate of negative nodes was seen ($P < .001$), while a consistent rate over time was seen for 1 or more positive nodes found ($P = .94$).

Trends in 2-year mortality by year of melanoma diagnosis are reported by both death from melanoma or metastases and death from all causes (Figure 3 and Table 1). While 2-year survival increased and 2-year case-fatality decreased over time (data not shown), the 2-year mortality rates by year of diagnosis were seen to increase over time. Trends in 2-year mortality from all cancer deaths (International Classification of Diseases, Ninth Revision, codes of 140-239) were parallel to those for melanoma and metastases, with an annual average of 0.3 per 100 000 more deaths (not shown). For 1973 through 1979
and 1980 through 1987, no significant trends were seen (Table 1). A lack of a linear trend from 1973 through 1987 can also be seen in Figure 3. For 1988 through 1992, a linear increase in death rates was seen. The largest increase was seen in death from melanoma or metastases of 8.6% annually or 39.3% over 5 years (Table 1).

<table>
<thead>
<tr>
<th>Disease Measure</th>
<th>Early Detection</th>
<th>Detection of Incidental Melanomas</th>
<th>Early Detection and Detection of Incidental Melanomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence</td>
<td>Temporary increase due to lead-time bias</td>
<td>Increase due to length bias</td>
<td>Temporary increase due to lead-time bias and overall increase due to length bias</td>
</tr>
<tr>
<td>Survival</td>
<td>Increase due to lead-time bias</td>
<td>Increase due to length bias</td>
<td>Increase due to lead-time bias and increase due to length bias</td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>Increase that stabilizes due to lead-time bias</td>
<td>Increase due to length bias</td>
<td>Increase due to lead-time bias and overall increase due to length bias (both should eventually stabilize)</td>
</tr>
<tr>
<td>Advanced-stage disease</td>
<td>Decrease due to lead-time bias</td>
<td>No change due to length bias</td>
<td>Decrease due to lead-time bias and no effect of length bias</td>
</tr>
<tr>
<td>Mortality</td>
<td>Decrease due to early detection</td>
<td>None</td>
<td>Decrease due to early detection</td>
</tr>
</tbody>
</table>

These results, based on nationwide US data, contain several potentially important findings. While it is well known that the incidence of melanoma has been increasing in various populations, these data suggest that the increase in melanoma incidence is not solely attributable to thin tumors. The proportion of tumors that are thick (more than 1 or 3 mm) was small; however, the rate of increase in incidence was higher (Table 2). This is particularly important because the 2-year and 5-year survival rates are lower for thick tumors (73% and 48%, respectively) than for all tumors, with survival rates of 88% and 75%, respectively. A previous study found that small melanomas were lethal in less than 5% of patients, whereas tumors of 4 mm or greater had a 50% case-fatality rate. The incidence of melanoma related to tumors with lymph node involvement remained constant over time. Overall, these data suggest that the increase in melanoma incidence over time is largely caused by an increase in localized-stage disease with no change in lymph node involvement but with thicker tumors.

No change in disease with lymph node involvement suggests that advanced melanoma is not changing, while an increase in thick tumors seen over time suggests that some severity of disease may be changing. Ultimately, we want to know if mortality rates from melanoma are changing. Since the SEER data are incidence data, they cannot be used to examine traditional mortality rates. The 2-year mortality by year of diagnosis reported in Figure 3 and Table 1 can be viewed as an incidence rate for fatal disease within 2 years of diagnosis. Figure 3 suggests that there was a higher rate of melanomas diagnosed in 1992 that lead to death within 2 years than there was in 1973.

Missing data do not usually occur at random. Tumor thickness had the highest percentage missing for any measure of severity. The survival rates of the missing data suggest that the missing group is a combination of the intermediate and large thickness groups (Table 2). This is similar to reports by SEER suggesting that cancer cases with missing stage in general tend to be regional- or distant-staged cases.

While the trends during 1973 through 1994 for regional, distant, and unstaged melanoma were not linear, based on Figure 1, the annual percentage changes based on the linear trend of 2.3%, 1.8%, and −1.0%, respectively, suggest that regional- and distant-stage disease have increased during the entire period while unstaged disease has decreased. Given the relative proportion of cases seen in Figure 1, the decrease in unstaged melanoma may account for any increases in regional or distant disease. The decrease in negative lymph nodes seems to be related to the increase in nodes not examined. This may reflect better clinical diagnosis as more melanomas are being seen. However, the data on lymph node involvement are inconclusive and should be interpreted with caution. No consistent patterns were seen for Clark levels of the melanoma tumors, possibly reflecting inconsistent coding for the extension of tumors in the data. Since the SEER data are not specifically coded into Clark levels and because of the increase over time in the number of cases with missing information needed to code Clark levels, few inferences from the Clark levels analyses can be made.

Increased surveillance of a disease will often affect the incidence, survival, and mortality of the disease. Table 3 describes the effect of increased surveillance on incidence, survival, and stage of melanoma, assuming no changes occurred in the natural course of the disease. Increased surveillance may create early detection of cancer, detect insignificant lesions, or both. Early detection of cancer creates a backward shift in the starting point for measuring survival, called lead-time bias. Early detection should reduce advanced disease while increasing early-stage disease. Regardless of whether treatment is available and effective, early detection will appear to lengthen survival because of lead-time bias. This apparent increase in both survival and incidence results from making the diagnosis earlier rather than from a true increase in either survival or incidence. Early detection should lead to an increase in the incidence of early-stage disease that levels off and slightly decreases a few years after mass screening is initiated, followed by a decrease in advanced disease. While mass screening for melanoma is not occurring in most US populations, increased surveillance may have a similar effect. However, increased surveillance of melanoma is likely to have occurred slowly over time, causing an increase in the incidence over a longer period, as has been seen in mela-
noma. Lead-time bias for melanoma in these data may be reflected in the significant increase in incidence of localized melanoma. However, the lack of a decrease in early-stage melanoma in later years suggests that lead-time bias is the least likely explanation. The likelihood of lead-time bias is further diminished by observation that the increase in early-stage melanoma was not followed by a decrease in advanced-stage melanoma as measured by distant-stage melanomas, thick melanomas, or positive nodes. Other studies show agreement, as they have not reported a decrease in advanced-stage melanoma or a decrease in thick melanomas.6-11

Increased surveillance may detect other nonaggressive disease states, referred to as clinically “insignificant” disease. These clinically insignificant or incidental melanomas are described as histologically malignant but biologically benign tumors.9 Incidental melanomas are lesions that theoretically would not have progressed into advanced disease or death but were detected by increased surveillance. Incidental melanomas represent length bias where increased surveillance is more likely to detect cancer that exists for longer periods (Table 3). Detection of incidental melanomas would increase survival and early-stage disease, which should slowly level off without decreasing but have no effect on mortality rates or advanced-stage disease (Table 3). These data are consistent with length bias caused by detection of clinically insignificant disease and are consistent with previous studies that do not support lead-time bias caused by early detection.7-12

Diagnosis of incidental melanomas or length bias does not account for the increase in thick tumors or the 2-year mortality seen for 1988 through 1994, suggesting that some of the increase in melanoma incidence is real. Similar increases in thick melanomas have not been seen in other studies.10,11 The increase in thin melanomas is possibly caused by increased surveillance but may reflect increased exposure to risk factors for melanoma. The increase in thicker melanomas is unexplained but may be related to the increase in mortality, which is supported by other studies.18 These increases suggest that some form of aggressive melanoma may be increasing in the population. If there is an increase in advanced melanomas caused by changes in risk factors or the disease, such an increase may have skewed any possible benefit of early detection of melanoma during 1973 through 1979. If there are various changes in melanoma going on, ie, early detection and treatment along with diagnosis of clinically insignificant melanomas and an increase in advanced disease, there is no way to separate the different effects.

These results suggest that there has been an apparent increase in melanoma incidence because of the detection of clinically insignificant melanomas and a real increase in advanced melanomas. The increase in thick melanomas may be an indication that the population is being exposed to increased ultraviolet radiation. Ultraviolet radiation has been implicated as a major risk factor associated with melanoma. Increased exposure to ultraviolet radiation is consistent with changes in lifestyles that may have produced increased exposure to the sun. Sun exposure plays a major role in the etiology of melanoma and has been increasing worldwide.10 Change in sun exposure in various populations is the most likely candidate for true increases in melanoma rates. Various studies suggest that childhood sun exposure and sunburns are important.20-23 However, the exact role of ultraviolet light in the pathogenesis of melanoma is unknown, and more conclusive research is needed.

Accepted for publication October 8, 1998.

This research was supported in part by grant 94C153394-0610 from the Cleveland Foundation, and Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio.

Reprints: Leslie K. Dennis, PhD, Department of Epidemiology and Biostatistics, R205A, Case Western Reserve University, MetroHealth Medical Center, 2500 MetroHealth Dr, Cleveland, OH 44109-1998 (e-mail: lkd3@po.cwru.edu).

REFERENCES