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Increasing Incidence of Melanoma Among Middle-Aged Adults: An Epidemiologic Study in Olmsted County, Minnesota

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Abstract

Objective: To identify changes in the incidence of cutaneous melanoma over time in the fastest-growing segment of the US population—middle-aged adults.

Patients and Methods: By using the Rochester Epidemiology Project resource, we identified patients aged 40 to 60 years who had a first lifetime diagnosis of melanoma between January 1, 1970, and December 31, 2009, in Olmsted County, Minnesota. The incidence of melanoma and overall and disease-specific survival rates were compared by age, sex, year of diagnosis, and stage of disease.

Results: Between 1970 and 2009, age- and sex-adjusted incidence increased significantly over time ($P<.001$) from 7.9 to 60.0 per 100,000 person-years, with a 24-fold increase in women and a 4.5-fold increase in men. Although not significant ($P=.06$), the incidence of melanoma increased with age. Overall and disease-specific survival improved over time, with hazard ratios of 0.94 ($P<.001$) and 0.93 ($P<.001$) for each 1-year increase in the year of diagnosis, respectively. Each 1-year increase in the age at diagnosis was associated with an increased risk of death from any cause (hazard ratio, 1.07; $P=.01$) but was not significantly associated with disease-specific death ($P=.98$). Sex was not significantly associated with death from any cause ($P=.81$) or death from disease ($P=.23$). No patient with malignant melanoma in situ died from disease. Patients with stage II, III, and IV disease were more than 14 times more likely to die from disease than were patients with stage 0 or I disease ($P<.001$).

Conclusion: The incidence of cutaneous melanoma among middle-aged adults increased over the past 4 decades, especially in middle-aged women, whereas mortality decreased.

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Skin cancer affects more people in the United States than does any other malignancy, with cutaneous melanoma (hereafter called melanoma) being particularly deadly. Melanoma is diagnosed in more than 75,000 Americans each year, and more than 9000 die from it annually.[1] Melanoma is the sixth most frequently diagnosed cancer in developed countries,[2] with the burden carried mainly by fair-skinned populations. It is within this demographic group that melanoma incidence is the highest and is well documented across Australia and New Zealand,[3,4] Europe,[5-9] and North America.[10,11] In the United States, the incidence of many common cancers, including prostate, colon, and breast cancer, either remains steady or has declined over time.[12] However, the incidence of melanoma steadily increases from year to year in non-Hispanic white men and women of all age groups and tumor thickness categories.[12,13] In addition, melanoma has previously been shown to have a higher incidence rate among women younger than 45 years and in men older than 45 years.[14,15]

The US Census Bureau in 2010 estimated that the group of residents aged between 45 and 64 years has grown more rapidly than any other age group during the preceding decade. Interestingly, this group of individuals has more than 50% of the cases of invasive melanomas diagnosed each year in the United States.[15] To our knowledge, there have been few true population-based epidemiology studies looking at the incidence of malignant melanoma in middle-aged men and women. The studies used to estimate the natural history, distribution

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of subtypes, incidence, and disease-related mortality of melanoma among the middle-aged population have been so far limited to those performed in populations that were not very well defined[16] or were biased by the underreporting and delayed reporting that characterize registry-based epidemiology studies.[17-19] Jemal et al[13] recently reported incidence rates of melanoma between 2002 and 2006 in the United States by using data from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute. They estimated incidence rates at 43.5 and 34.0 per 100,000 persons for men and women aged between 40 and 64 years, respectively. The calculated annual percent change in incidence rates from 1992 to 2006 was 3.0%.[13] In 2012, Reed et al[14] estimated the true age- and sex-specific incidence of melanoma from 1970 through 2009 in Olmsted County, Minnesota, in patients aged 18 to 39 years. They found that melanoma among young adults is increasing rapidly, especially among women. The current study aimed to estimate the true age- and sex-specific incidence of melanoma in adults aged 40 to 60 years in Olmsted County over the same period. Univariable and multivariable associations of select features with death from melanoma were assessed in this same population.

PATIENTS AND METHODS

Patient Selection

After approval by the institutional review boards of Olmsted Medical Center and Mayo Clinic, 383 adults aged 40 to 60 years who were residents of Olmsted County, Minnesota, at their first lifetime diagnosis of cutaneous melanoma between January 1, 1970, and December 31, 2009, were identified by using the resources of the Rochester Epidemiology Project (REP).[20] The REP was created in 1966, when indexes of diagnoses were created for use by medical professionals in Olmsted County, Minnesota. The result is linkage of medical data from almost all sources of medical care available to the local population of the county. According to the US Census, Olmsted County had a population of 144,000 people in 2010. The majority are non-Hispanic white persons who are socioeconomically similar to the general white population, despite a higher percentage of college graduates in Olmsted County.[21] Approximately 95% of the residents of Olmsted County have given permission to use their medical records for research purposes. The REP allows researchers to estimate the true incidence for almost any disease in the population.[22]

Statistical Analyses

Incidence rates per 100,000 person-years were calculated overall and by decade by using incident cases of melanoma as the numerator and age- and sex-specific estimates of the population of Olmsted County, Minnesota, as the denominator. The population at risk was estimated by using US Census data from 1970, 1980, 1990, and 2000, with linear interpolation for intercensal years. Incidence rates were age- and sex-adjusted to the structure of the 2000 US white population.

The relationships between the incidence of melanoma and age at diagnosis, sex, and calendar year of diagnosis were assessed by fitting generalized linear models by using the SAS procedure GENMOD (SAS Institute, Inc). Incident cases were grouped into 4 age intervals (40-44, 45-49, 50-54, and 55-60 years) and 4 calendar-year intervals (1970-1979, 1980-1989, 1990-1999, and 2000-2009). The models fit the natural logarithm of crude incidence rates as a linear function of age at diagnosis, sex, and calendar year of diagnosis, with a Poisson distribution used to model the error structure. The significance of the linear trends for the features of interest and interaction terms among these features was assessed by using likelihood ratio statistics.

Changes in features by decade of diagnosis were evaluated by using Kruskal-Wallis and trend tests. Overall survival and disease-specific survival rates were estimated by using the Kaplan-Meier method. The duration of follow-up was calculated from the date of diagnosis to the date of death or last follow-up. Univariable and multivariable associations with death from any cause and death from disease were evaluated by using Cox proportional hazards regression models and summarized with hazard ratios and 95% CIs. The covariates used in the multivariable models included year of diagnosis, age at diagnosis, sex, and pathologic stage.

All analyses were performed by using the SAS software package (version 9.2), and *P* value of less than .05 was considered statistically significant.

TABLE 1. Summary of Characteristics (N=383)[a,b]

Feature	Value
Age at diagnosis (y)	49.6 (49; 40-60)
Exact Breslow thickness (n=288) (mm)	0.95 (0.54; 0.10-14.00)
Sex and site	
Women	181 (47)
Head/neck	19 (11)
Trunk	51 (28)
Upper limb	54 (30)
Lower limb	57 (31)
Men	202 (53)
Head/neck	46 (23)
Trunk	84 (42)
Upper limb	49 (24)
Lower limb	20 (10)
Unknown	3 (1)
Decade of diagnosis	
1970-1979	13 (3)
1980-1989	41 (11)
1990-1999	102 (27)
2000-2009	227 (59)
Location (n=378)	
Left	173 (46)
Right	170 (45)
Central	34 (9)
Bilateral	1 (<1)
Breslow thickness (n=362) (mm)	
≤1.00	304 (84)
1.01-2.00	35 (10)
2.01-4.00	15 (4)
>4.00	8 (2)
Base transected	13 (3)
Clark level (n=368)	
I	76 (21)
II	177 (48)
III	66 (18)
IV	44 (12)
V	5 (1)
Margins at initial incision (n=325)	
Negative	221 (68)
Positive	104 (32)
Histogenic type (n=318)	
SS	209 (66)
SS in situ	3 (1)
Nodular	21 (7)
LM	18 (6)
LM in situ	12 (4)
MMIS	52 (16)
Acral lentiginous	3 (1)
Preexisting nevus (n=311)	
Absent	209 (67)
Nevus NOS	62 (20)
CN	22 (7)
DN	18 (6)
Pathologic stage (n=373)	
0	69 (19)
IA	239 (64)
IB	33 (9)
IIA	7 (2)
IIB	8 (2)
IIC	1 (<1)
III	1 (<1)
IIIA	5 (1)
IIIB	3 (1)
IIIC	1 (<1)
IV	6 (2)

[a]CN = compound nevus; DN = dermal nevus; LM = lentigo maligna; MMIS = malignant melanoma in situ; NOS = not otherwise specified; SS = superficial spreading.
[b]Values are mean (median; range) or No. (percentage).

RESULTS

By using REP resources, we identified 383 middle-aged adults aged 40 to 60 years who had their first lifetime diagnosis of melanoma between 1970 and 2009. Characteristics of the 383 adults under study are summarized in Table 1. Demographic characteristics include body distribution of melanoma, with the trunk (back) being the most commonly affected region of the body in men and the lower limbs (leg) in women. For this study, histologic slides were not examined to confirm diagnosis, because histologic examination of melanomas from previous REP incidence studies of young adults showed no discrepancies.[14]

The overall age- and sex-adjusted melanoma incidence rate for the adults studied was 37.1 per 100,000 person-years. Incidence rates by age and decade at diagnosis are illustrated in Figure 1. Age-adjusted incidence rate was similar for women and men (34.5 and 39.8 per 100,000 person-years, respectively; $P=.16$). The incidence appeared to increase with age but was not statistically significant ($P=.06$). Interestingly, however, the incidence increased significantly by decade of diagnosis ($P<.001$) for both women and men. Age- and sex-adjusted incidence rate increased from 7.9 per 100,000 person-years in the period 1970 to 1979 to 60.0 per 100,000 person-years in the period 2000 to 2009, a 7.6-fold increase, with a 24-fold increase in women and a 4.5-fold increase in men. There were no statistically

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significant interactions among age at diagnosis, sex, and decade of diagnosis (Table 2).

Among the 373 patients with pathologic stage available, 69 (18%) were classified as having stage 0 disease at diagnosis, 272 (73%) as stage I disease, and 32 (9%) as stage II, III, or IV disease. Incidence rates by stage are summarized in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) and illustrated by decade of diagnosis and age at diagnosis in Figure 2.

A comparison of select features by decade is shown in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). The first 2 decades were combined because only 13 patients received a diagnosis of melanoma in the period 1970 to 1979 (and fewer than 13 had complete data). There was evidence that Breslow thickness and pathologic stage decreased significantly over time.

At last follow-up, 52 patients had died at a mean of 7.1 years after diagnosis (median, 3.2 years; range, 0.1-30.6 years). Among the 331 patients still alive at last follow-up, the mean duration of follow-up was 9.9 years (median, 7.6 years; range, 0.1-37.1 years). Estimated overall survival rates (95% CI; number still at risk) at 5, 10, 15, and 20 years after diagnosis were 92% (89%-95%; 239), 87% (83%-91%; 140), 82% (76%-88%; 75), and 77% (70%-85%; 40), respectively. Univariable and multivariable associations of select features with death from any cause are summarized in Table 2. In a multivariable setting, each 1-year increase in the calendar year of diagnosis was associated with a statistically significantly decreased risk of death from any cause (hazard ratio, 0.94; $P<.001$) while each 1-year increase in the age at diagnosis was associated with a 7% increased risk of death from any cause (hazard ratio, 1.07; $P=.01$). There was no significant difference in death from any cause between women and men ($P=.81$).

Among the 52 patients who died, 34 died from melanoma, 17 died from other causes, and 1 had an unknown cause of death and was therefore excluded from analyses of disease-specific survival rates. Estimated disease-specific survival rates (95% CI; number still at risk) at 5, 10, 15, and 20 years after diagnosis were 93% (91%-96%; 239), 90% (86%-94%; 140), 88% (84%-92%; 75), and 86% (81%-92%; 40), respectively. Univariable and multivariable associations of select features with death from disease are summarized in Table 2. In a multivariable setting, each 1-year increase in the calendar year of diagnosis was associated with a statistically significantly decreased risk of death from melanoma (hazard ratio, 0.93; $P<.001$). Age ($P=.98$) and sex ($P=.23$) were not significantly associated with death from disease in a multivariable setting. No patient with stage 0 melanoma died from the disease; therefore, stage 0 could not be used as reference group in a Cox proportional hazard regression model. As such, patients with stage 0 and stage I disease were combined for analysis. Patients with stage II, III, or IV disease were more than 14 times more likely to die from melanoma than were patients with stage 0 or I disease (hazard ratio, 14.40; $P<.001$). Disease-specific survival by stage and decade of diagnosis is illustrated in Figure 3.

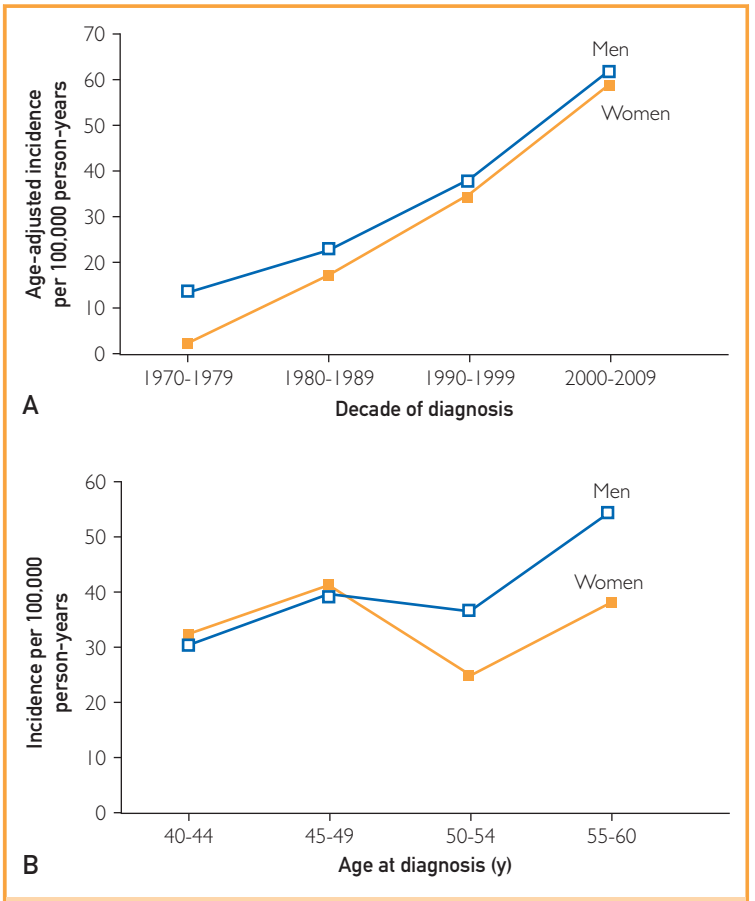

FIGURE 1. Incidence per 100,000 person-years age-adjusted to 2000 US white population rates. A, By decade of diagnosis. B, By age.

TABLE 2. Associations With Death From Disease (n=382) and Death From Any Cause (N=383)

Feature	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Associations with death from disease				
Year of diagnosis	0.92 (0.89-0.95)[a]	<.001	0.93 (0.90-0.96)[a]	<.001
Age at diagnosis (y)	1.02 (0.96-1.08)[a]	.53	1.00 (0.94-1.06)[a]	.98
Sex				
Female	1.0 (Reference)		1.0 (Reference)	
Male	2.16 (1.03-4.52)	.04	1.58 (0.75-3.35)	.23
Pathologic stage (n=372)				
0, I	1.0 (Reference)		1.0 (Reference)	
II, III, IV	17.76 (8.92-35.35)	<.001	14.40 (7.10-29.23)	<.001
Associations with death from any cause				
Year of diagnosis	0.93 (0.91-0.96)[a]	<.001	0.94 (0.91-0.97)[a]	<.001
Age at diagnosis (y)	1.07 (1.02-1.12)[a]	.004	1.07 (1.02-1.12)[a]	.01
Sex				
Female	1.0 (Reference)		1.0 (Reference)	
Male	1.49 (0.85-2.63)	.16	1.07 (0.60-1.91)	.81
Pathologic stage (n=373)				
0	1.0 (Reference)		1.0 (Reference)	
I	6.53 (0.89-48.10)	.07	5.38 (0.73-39.82)	.10
II, III, IV	63.78 (8.54-476.45)	<.001	43.74 (5.80-330.14)	<.001

[a]Hazard ratio represents a 1-y increase.

DISCUSSION

The results of this population-based study confirm that the incidence of melanoma is increasing in the middle-aged population, the fastest-growing segment of our society, despite reports to the contrary.[18,23] The incidence rose 7.6-fold from the 1970s to the 2000s in Olmsted County, Minnesota, with increasing rates for all tumor thickness categories among our study population. The dramatic rise in the incidence of melanoma was seen mainly in stage 0 and I tumors for both men and women during the study period, which is in line with data reported for non-Hispanic white persons across Europe and Australia.[7,24] Women had 3 times higher incidence rates of malignant melanoma in situ in the last decade. Stage I melanomas were equivalent between sexes, and the deeper Breslow depth lesions tended to occur more frequently in men. However, our study did not have the numbers to make statistically meaningful comparisons between men and women for deeper melanomas. As has been published in the young adult population,[14] rates rose more dramatically among women, in whom the incidence increased by 24-fold; for men, the incidence increased by 4.5-fold. Although not statistically significant (*P*=.06), the incidence of melanoma increased with age in both men and women; rates were higher in women aged 50 years or younger and much higher in men after this age (Figure 1).

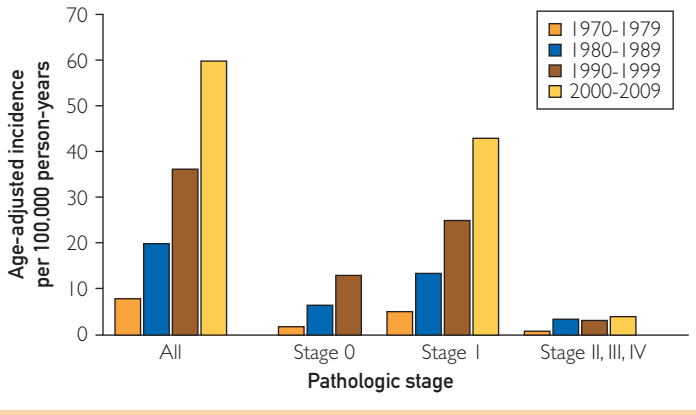

FIGURE 2. Age-adjusted incidence per 100,000 person-years by pathologic stage.

The convergence and parallel nature of incidence rates in the middle-aged population for women and men was not entirely expected (Figure 1) because recently published data suggest a divergence of incidence rates among women and men in the middle-aged population, with men demonstrating age-related increases

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with time.[13,15] The higher rates of melanoma in women tend to parallel the years before menopause.[14,25] In this study, women aged 50 years or younger tended to have higher rates of melanoma, suggesting a potential hormonal effect during these years. The reason(s) behind this is not clear. However, these are the years when previous tanning bed use and ultraviolet exposure in the preceding 1 or 2 decades may have influenced the development of melanoma. The relationship between ultraviolet exposure and melanoma is well documented in the literature. A meta-analysis confirmed the association between the use of tanning beds and melanoma.[26] Studies are ongoing at our institution to better define and explore potential hormonal effects in the development of melanoma.

The rates of cutaneous melanoma are clearly increasing over time, yet the disease-specific mortality has remained relatively stable and is decreasing in our study population.[13] Our results are similar to those reported in central Europe and Australia, namely, thinner, less-invasive melanomas, especially since the 1980s.[24] Some argue that thin melanomas are the result of more liberal diagnostic criteria and are biologically insignificant, concluding that the melanoma epidemic is simply due to overdiagnosis.[27,28] Ackerman et al[29] were the first to attribute the increase in melanoma incidence to better diagnostic criteria. Their group published the first study to focus on histopathologic criteria for the diagnosis of melanoma "formulated on the basis of proven metastatic lesions" in the mid-1970s,[30] the same decade in which melanoma rates began to increase substantially. The refinement of these criteria has led to more uniform teaching and application across the world. Moreover, earlier detection through educational programs, more skin cancer screenings, and increased public awareness, together with longer human lifespan and more dermatologists using improved clinical diagnostic algorithms for biopsy (which now includes dermoscopy), provide reasonable explanations for the divergence of incidence and mortality rates.[14,31]

Identifying melanoma before it has had a chance to invade or early in the invasion process undoubtedly leads to increased survival. Some would highlight this as a reason for the overdiagnosis of melanoma, concluding that thin melanomas are morphologically malignant but biologically benign.[32] In 1975, Clark et al[33] argued that there was no biologic evidence to suggest that malignant melanoma in situ is a malignant disease. Our multivariable models, including year of diagnosis and stage, indicate that even after adjusting for stage, survival improved over time (Table 2). Likewise, after adjusting for improvement in survival over time, patients with high-stage disease were significantly more likely to die. In the middle-aged population, increasing rates are largely confined to melanomas thinner than 1 mm, yet recent data suggest that thin melanomas still represent 24% to 30% of disease-specific deaths.[13,34] Our results also showed that a quarter of melanoma-related deaths occurred in those with thin melanomas. Furthermore, we report an increasing incidence of not only thin melanomas but also all tumor thickness categories and subtypes,

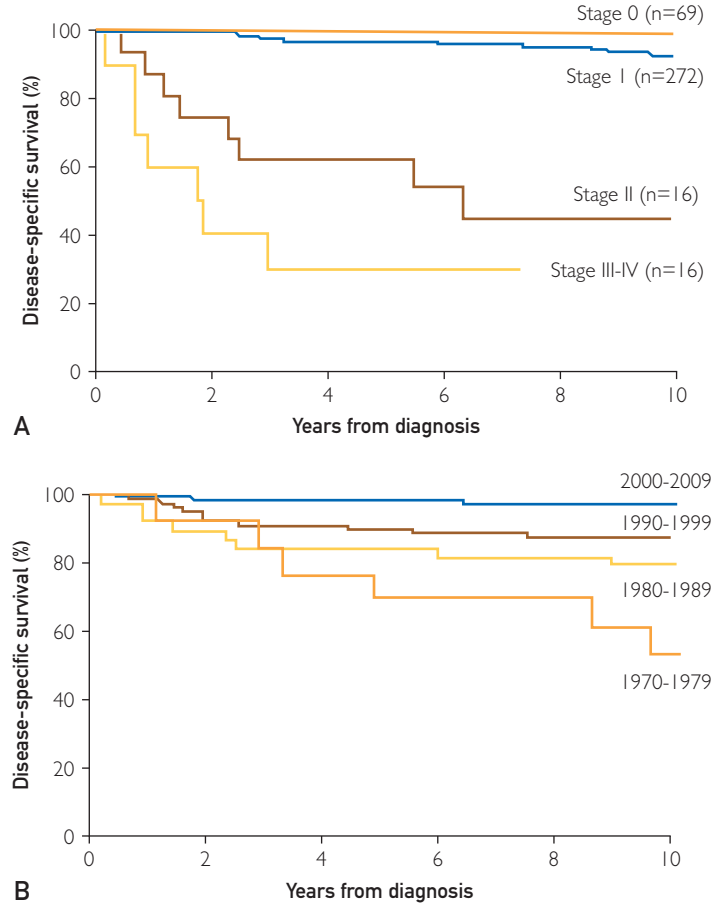

FIGURE 3. Disease-specific survival by (A) stage (log-rank test, $P<.001$) and (B) decade (log-rank test, $P<.001$).

which confirms recent Surveillance, Epidemiology, and End Results program data showing similar increases in the 70,000 new cases of malignant melanoma from 1992 to 2004.[11] We believe that all this evidence, together with the data reported here, is sufficient to suggest a true increase in the incidence of melanoma and not a phenomenon of overdiagnosis.

In our study population, men tended to have thicker melanomas and experienced poorer outcomes than did women. Studies suggest that men are more likely to experience sunburns and have outdoor occupations and are less likely to use sunscreen,[35] conduct skin self-examinations,[36,37] or use melanoma screening programs.[38,39] Invasive tumors are more prevalent in lower socioeconomic populations, in whom access to health care is poor and the availability of skin cancer screening is limited.[34] The residents of Olmsted County, Minnesota, have relatively effortless access to health care. This variable remained constant throughout the duration of the study and may help explain why most patients had early-stage disease at the time of presentation. Mortality, as expected, was strongly associated with increased Breslow depth and advanced-stage disease. In our study, the incidence of advanced-stage melanoma remained constant over 4 decades (Figure 2); however, disease-specific mortality decreased substantially with each decade studied, most notably the last 10 years of the study (Figure 3).

A limitation of this study is the incomplete and accurate reporting of melanoma within medical records. However, it is unlikely that incident cases were missed because final diagnoses from pathologic specimens are input into Olmsted County medical records. The population of Olmsted County may be another potential limitation because the majority of the population studied was white and well educated, with ready access to health care. Thus, care should be taken when extrapolating the results of this study to other subpopulations in the United States.

CONCLUSION

The incidence of cutaneous melanoma increased significantly over the past 4 decades in Olmsted County, Minnesota, with women experiencing higher rates of increase than did men. Although the incidence of melanoma is increasing, death from disease seems to be decreasing with time. Close monitoring of middle-aged patients with regular skin cancer screening examinations is strongly recommended.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviation and Acronym: **REP** = Rochester Epidemiology Project

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