Title

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Journal

JAMA Dermatology, 149(8)

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Publication Date

2013-08-01

DOI

10.1001/jamadermatol.2013.4581

Peer reviewed

Published in final edited form as:
JAMA Dermatol. 2013 August ; 149(8): . doi:10.1001/jamadermatol.2013.4581.

Survival for patients with single and multiple primary melanomas in the GEM study

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Kricker, Armstrong, Goumas, Thomas, From, Busam, Kanetsky, Gallagher, Marrett, Groben, Gruber, Anton-Culver, Rosso, Berwick.
Drafting of the manuscript: Kricker, Armstrong.
Critical revision of the manuscript for important intellectual content: all authors. *Statistical analysis:* Kricker, Armstrong, Goumas, Thomas.
Obtained funding: Kricker, Armstrong, Thomas, From, Gallagher, Marrett, Gruber, Anton-Culver, Berwick.
Study supervision: Kricker, Armstrong, Thomas, From, Gallagher, Marrett, Gruber, Anton-Culver, Rosso, Berwick.

Financial disclosure: None reported.

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Abstract

Objective—Little is known about survival after a diagnosis of a second or higher order (multiple) primary melanoma. We aimed to determine whether survival after diagnosis was better in patients with multiple primary melanomas (MPM) than with single primary melanomas (SPM), as suggested in a recent study.

Design—Survival analysis with median follow-up of 7.6 years (range 0.4-10.6).

Setting—The Genes, Environment and Melanoma (GEM) study enrolled incident cases of melanoma notified to population-based cancer registries in Australia, Canada, Italy and the USA. MPM were ascertained over a longer period than SPM.

Participants—2372 patients with SPM and 1206 with MPM.

Main outcome measures—Melanoma-specific fatality hazard ratios (HR) and confidence intervals (CI) associated with clinical and pathologic characteristics of SPM, MPM and both together in Cox regression models.

Results—Thickness was the main determinant of fatality (HR for >4mm=7.68, 95% CI 4.46 to 13.23); other independent predictors were ulceration, mitoses and scalp location. After adjustment for these other predictors, there was little difference in fatality between MPM and SPM (HR for MPM relative to SPM=1.24, 95% CI 0.91 to 1.69; $P = .18$). Thicker SPM, however, had higher fatality (HR for >4mm=13.56, 95% CI 6.47-28.40) than thicker MPM (HR for >4mm=2.93, 95% CI 1.17-7.30).

Conclusion—While overall fatalities from SPM and MPM were similar, relative fatality for thick SPM was greater than for thick MPM. This finding may offer support for a difference in outcome between patients with SPM and MPM that is worth further exploration.

Keywords

GEM; MPM; SPM; pathology characteristics; fatality; survival

INTRODUCTION

Subsequent melanomas in patients with multiple primary melanomas are well known to be thinner, on average, than prior melanomas and might therefore have a better outcome.[1-3] Whether survival is better or worse for patients diagnosed with multiple primary melanomas (MPM) than a single primary melanoma (SPM) is important for prognosis. Results from earlier studies examining survival of SPM and MPM offer little consistent information; they had few patients, limited analysis to selected stage categories, or presented crude survival estimates only.[4-7] A recent assessment based on 4952 SPM and 298 MPM melanoma clinic patients with stage 1 or 2 disease, however, suggested that patients with multiple primary melanomas survived longer than those with a single primary melanoma after taking account of other prognostic factors.[8] Among possible mechanisms for an apparent survival benefit, the authors discuss whether multiple melanomas may provoke a stronger host immune

response,[8] which might also explain better survival for MPM than SPM after diagnosis of metastatic disease.[9] Additionally, the possibility that both initial and subsequent melanomas are thinner in MPM than SPM has given rise to speculation that MPM may be biologically different from SPM.[2,10]

No study has yet explored survival in a population-based sample that included patients with single and patients with multiple primary melanomas of any stage. Our analysis was undertaken to determine whether survival after diagnosis with MPM was better than after diagnosis with SPM in the large, population-based Genes, Environment and Melanoma (GEM) study. Specifically, we analyze detailed pathologic features of the melanomas to identify their contribution to overall survival and to survival in MPM and SPM separately, and to explore whether differences in these contributions suggest biological differences between MPM and SPM that affect outcome.

METHODS

GEM enrolled incident cases of primary melanoma registered in population-based cancer registries in Australia, Canada, Italy and the USA (see[1,11]). Briefly, SPM were diagnosed with a first invasive primary melanoma in 2000 and MPM with a second or higher order invasive or in situ melanoma in 1998-2003 (referred to as the recent MPM); all patients provided written informed consent. Institutional Review Boards at the Memorial Sloan–Kettering Cancer Center, New York, and each contributing centre approved the study protocol.

A total of 2372 SPM and 1206 MPM were eligible for the survival analyses. Breslow thickness and anatomic site were abstracted from community pathologists' and expert review reports[1] while ulceration and mitoses were available only from the latter; more SPM (87%) than recent (79%) or prior MPM (65%) had slides available for review. Information on nodal metastases was unavailable. Among other items, patients were asked at interview for education, used as a surrogate for socioeconomic status in these analyses, and history of melanoma in first degree relatives.

We analyzed melanoma-specific survival in SPM and MPM patients by tumor pathology characteristics. For MPM patients we included in the analysis the pathology characteristics of the melanoma considered most likely to cause death, which was selected using an algorithm based on stage at and time between diagnosis of the melanomas (see, for example[9]). Characteristics of the recent MPM were used in statistical models when melanomas were diagnosed more than 5 years apart, except when the most recent MPM was in situ, since the prior melanoma is less likely to be responsible for clinical outcome in patients who survive 5+ years after diagnosis. For melanomas less than 5 years apart, the characteristics of the MPM with the highest known AJCC tumor stage were used. When both melanomas were <=1mm thick, the presence of mitoses was considered to indicate the higher stage. Patient follow-up to ascertain deaths finished at the end of 2007 in most centres and 2008 in British Columbia and Torino.

Age at diagnosis of SPM or the selected MPM was designated the 'age at diagnosis' for analysis. Cumulative percentage incidence and mortality was plotted by 5 year age groups to investigate the apparent rarity of deaths at younger ages in MPM than SPM. For survival analyses, melanoma-specific survival time was accumulated from the diagnosis date of the SPM or the most recent MPM to melanoma death; all other cases were censored at the end of follow-up or at death from other causes. Kaplan-Meier methods were used to estimate survival proportions in SPM and MPM separately and test for differences using the log rank test. We used Kaplan-Meier methods also to estimate survival proportions in SPM and

MPM separately and to construct survival curves for all SPM and MPM by thickness (≤2mm, >2mm) and age (<70, 70+ years) and tested the associations between survival and these factors using the log rank test; all *P* values were <0.05 for difference between the two.

Hazard ratios (HR) and 95% confidence intervals (CI) associated with SPM or MPM status, Breslow thickness, Clark level, presence of vertical growth, ulceration, mitoses and site were estimated in Cox proportional hazard regression models for all SPM and MPM including, as covariates, age as a continuous variable, sex and study center. To display the influence of age we present estimates for age grouped in decades. Cases with missing values were included in these models using missing values categories for relevant variables. We constructed a variable for AJCC tumor sub-stages using thickness and ulceration or mitoses to define stage 1 and thickness and ulceration for stages 2, 3 and 4. Information on metastases was unavailable.

We also estimated HRs associated with SPM or MPM status, thickness, ulceration, mitoses and site in multivariable models for all SPM and MPM, adjusted for age, sex, center, and including education and family history as potential confounders; the models excluded patients with missing information except where family history was missing, for which a missing value category was used to retain 6% of patients lacking this information. To assist in evaluating whether there was a difference in effect estimates for each of thickness, ulceration, mitoses and site by SPM or MPM status, we estimated *P* values for interaction, using the Wald test to compare the multivariable model with main effects only with a model with main effects and the cross-product term.

The associations of pathology variables with survival were evaluated separately for men and women and separately also for SPM and MPM, and we examined the influence of time between MPM using three time intervals (<3 months, 3 months to 5 years, >5 years). All *P* values were two sided and $P < .05$ was considered statistically significant. Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves in STATA/SE 8.2 showed little evidence that the proportional hazards assumption was violated. SAS software version 9.1 was used for all other statistical analyses.

RESULTS

A total of 563 deaths occurred including 255 deaths from melanoma, 152 SPM and 103 MPM deaths. The median follow-up times were 8 years from diagnosis of an SPM and 6.6 years from diagnosis of the most recent MPM (7.6 years for all patients, range 0.4-10.6 years). Kaplan Meier survival estimates were more favorable at 7 years for SPM than MPM (93.8% vs 90.3%; $P=.001$) although they were identical at 3 years (97.2%) and very similar at 5 years (95.1% SPM, 94.1% MPM). Compared with SPM, dates of diagnosis of the most recent MPM and death from melanoma were shifted towards older ages; there were no deaths before age 50 in MPM (Figure 1). MPM patients were older (mean age 62.9 years, range 7 to 95) than SPM patients (mean age 54.8 years, range 9 to 97) and the mean age at death was 65 years (range 23–93) in SPM and 73 (55–90) in MPM. MPM were more likely to be in men (66% M, 34% F) than SPM (52% M, 48% F) and men had more >2mm MPM than women (73% M, 27% F).

The most recent MPM was generally thinner than the previous one[1] although >4mm lesions were as likely in MPM (5%) as SPM (5%; $P=.7$). The average tumor size in men was similar for SPM and MPM (1.45mm and 1.43mm; $P=.11$) but women had thicker SPM than MPM (1.20mm SPM, 1.11mm MPM; $P<.001$).

As a preliminary to comparing survival in SPM and MPM, we analyzed effects of other clinical and pathologic factors on survival in models including age, sex, and study center.

Deeper invasion, whether assessed by Breslow thickness, Clark level or presence of vertical growth increased risk of melanoma death strongly (eTable 1). Unadjusted 5 year survivals for >2mm melanomas were 72% at 70+ years and 84% at <70 years and similar for men and women although deaths were rare in women aged <70 (Figure 2).

We constructed a multivariable model to include all variables with *P*<.1 in single variable analyses, adjusted for age, sex, center, and including family history and education; the multivariable model included 2770 patients with complete information. Increasing thickness (HR for >4mm=7.68, 95% CI 4.46-13.23), ulceration, presence of mitoses and scalp location (HRs up to 2.25) were each independently associated with increased melanoma fatality (*P*<.05 in each case), and age <40 years with reduced risk (HR=0.44, 95% CI 0.23-0.84) (Table 1). There was statistical evidence that the relationship between thickness and fatality was different for SPM and MPM (*P* for interaction .004), but not between ulceration or mitoses and fatality. Although fatality was much less in women when adjusted for age and center only (HR=0.56, 95% CI 0.43-0.75, relative to men), there was no evidence of a difference in fatality in the fully adjusted model (HR=0.86, 95% CI 0.62-1.20). In separate analyses for men and women, the patterns of increasing risk with increasing thickness and an increased HR with ulceration were also present, while mitoses increased fatality in men (by 80%) but not in women (data not shown).

The HRs for AJCC tumor "b" substages were around 1.5-2 fold higher than for "a" substages for each thickness category, relative to melanomas ≤1mm with no ulceration or mitoses (Table 2). The patterns of risk by AJCC tumor stage were very similar in separate analyses in men and women as in both sexes combined (data not shown). Fewer women than men had ulcerated MPM (5% of all melanomas in F, 9.3% in M); 5 year survival proportions by ulceration in both sexes were 77% with ulceration and 96% in its absence.

When we examined SPM and MPM in separate multivariable models, fatality of SPM increased with increasing thickness to HR=10.45, 95% CI 5.21-20.97 for 2.01-4mm and HR=13.56, 95% CI6.47-28.4 for >4mm. For MPM, however, HRs for all categories of thickness were around 2.6-2.9 and had no evidence of a trend (eTable 2). Ulceration and mitoses had HRs between 1.5 and 2.0 for each of SPM and MPM but the estimates were statistically significant only for ulceration in SPM and mitoses in MPM. Melanoma on the scalp increased risk 2.5-fold and age <60 at diagnosis reduced risk substantially for each of SPM and MPM.

There was no evidence of variation in fatality of MPM by time interval between the melanomas (results not shown).

DISCUSSION

Contrary to Doubrovsky and Menzies' finding of more favorable survival for MPM than SPM after controlling for prognostic factors,[8] we found the fatality after a diagnosis of MPM to be overall a little higher than that after a diagnosis of SPM, but not significantly so. Our study though was population-based and included melanomas of any stage, theirs included stages 1 and 2 only. Thickness was the most important determinant of survival in GEM patients with SPM and with MPM, as it is for melanoma generally.[12,13] Ulceration and the presence of mitoses among pathology characteristics and location on the scalp were also independently associated with increased fatality of both as was increasing age.

Thickness is a well-established prognostic factor for survival in primary melanomas, with relative survival proportions of 50% for 4+mm but nearly 100% for <0.75mm melanomas at 5 and 10 years after diagnosis.[12] Similarly in GEM, survival was much poorer for >4mm than ≤1 mm thickness and additionally, we observed a relative risk of death following a

>4mm melanoma that was 4.6 times higher for SPM than MPM despite similar proportions of >4mm lesions in SPM and MPM patients. Doubrovsky and Menzies reported a significant effect of thickness on melanoma death in their study but did not report on SPM and MPM separately.[8] Another study investigated whether a less aggressive biology in MPM, represented by mitotic rate, was a possible explanation for the generally thinner lesions in MPM and SPM but concluded that it was not and that other factors such as increased surveillance or genetic constitution probably contribute.[10]

We evaluated the prognostic significance for SPM and MPM of a number of other pathologic factors known to be associated with a poor outcome in primary melanomas. Risks of death were higher for a given thickness in the presence of ulceration than in its absence, in consistency with the increased severity ulceration confers at each stage in AJCC melanoma tumor staging definitions.[14] In GEM, ulceration was as likely in SPM and MPM (7% and 8% respectively), as elsewhere,[15] but we found little evidence of a difference between SPM and MPM in its effect on survival. Similarly, mitotic rate is an accurate and independent predictor of survival,[14,16-20] but its effect was also little different between SPM and MPM. That similar mitotic rates have been observed for SPM and MPM suggests little difference in underlying biologic aggressiveness between SPM and MPM lesions.[10]

We also examined other clinical factors. A poorer outcome for scalp than facial sites, usually in older men,[12,21,22] has not been investigated fully in previous relevant MPM studies[4,8] but is considered to be due to tumor factors.[12,20-22] Scalp melanomas in GEM were similarly fatal in SPM and MPM and apparently had a higher fatality in women than men, consistent with possible late stage diagnosis in women (35% of scalp SPM in women were >2mm).

Survival was more favorable in younger people in our study and worsened with increasing age. Age 70+ years is suggested to worsen melanoma prognosis,[12,16,17,23] an outcome that is independent of thicker lesions in older patients,[24] probably because age is a surrogate for a declining host defense system.[14,17]

The poorer survival in men than women reported for primary melanomas[12] is suggested to be due to late stage diagnosis in men.[23,25] We found limited evidence, however, for poorer outcomes in men in our data, mainly that survival was somewhat poorer for thicker melanomas in men (see Figure 2), and they had more melanomas with ulceration. The relatively small number at age 70+ of women with MPM (24% of MPM in women) is not unexpected, given that melanoma incidence at older ages is lower in women than men (http://seer.cancer.gov/csr/1975_2007/).

Major strengths of our study are the population-based ascertainment, the extensive clinicopathologic information on prognostic variables and the expert pathologic review for many slides.[1] Information on ulceration and mitoses was missing more often for MPM than SPM (32% missing vs 18%) because pre-2000 tumors, many of which were prior MPM, were more often unavailable for expert review (45% post 1999 vs 19% pre-2000; p<.001). It may be a weakness also that GEM did not identify SPM patients who had another melanoma diagnosed between the close of initial study enrolment and the end of followup. The resulting misclassification of SPMs as MPMs would have tended towards reducing any observed difference between them in overall fatality and in fatality associated with >4mm lesions. The study also lacked information about nodal or metastatic disease at diagnosis and time to relapse or recurrence. The different health care systems in place in GEM centers in the USA, Canada, Italy and Australia could have been a source of differences in access to diagnosis or care for patients. We sought to address this issue by including center as a

covariate in all analyses and additionally, education as a surrogate for socioeconomic status in all multivariable models.

In summary, we found no strong evidence of a difference in survival between SPM and MPM, despite the evidence of others[8] and suggestions that MPM may have a less aggressive biology than SPM.[2,8,10] We report for the first time, however, a greater increase in risk of death with increasing tumor thickness for SPM than MPM: this was the main feature that indicated a possible difference between outcome in patients with single or multiple melanomas.

Doubrovsky and Menzies reported that an increasing number of melanomas influenced survival favorably.[8] They suggested that the effects of immunological surveillance against melanomas may be substantial in MPM patients.[8] The results of our study suggest that preference be given to further investigation of this hypothesis over effects simply of closer surveillance and earlier diagnosis as a potential explanation for generally thinner lesions, and an apparently better outcome for the thickest lesions, in MPM than SPM patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The study was conducted by the GEM Study Group: Marianne Berwick (PI, University of New Mexico), Memorial Sloan-Kettering Cancer Center, New York, NY, USA: Colin Begg (Co-PI), Irene Orlow (Co-Investigator), Urvi Mujumdar (Project Coordinator), Klaus Busam (Dermatopathologist), Pampa Roy (Laboratory Technician). *Study Centers*: The University of Sydney and The Cancer Council New South Wales, Sydney (Australia): Bruce Armstrong (PI), Anne Kricker (co-PI), Melisa Litchfield (Study Coordinator). Menzies Research Institute, University of Tasmania, Hobart (Australia): Terence Dwyer (PI, currently at the International Agency for Research on Cancer, Lyon, France), Paul Tucker (Dermatopathologist), Alison Venn (co-Investigator), Nicola Stephens (Study Coordinator). British Columbia Cancer Agency, Vancouver (Canada): Richard Gallagher (PI), Teresa Switzer (Coordinator). Cancer Care Ontario, Toronto (Canada): Loraine Marrett (PI), Elizabeth Theis (Co-Investigator), Lynn From (Dermatopathologist), Noori Chowdhury (Coordinator), Louise Vanasse (Coordinator). Piedmont Cancer Registry, Cancer Prevention Center, Turin (Italy): Stefano Rosso (PI), Roberto Zanetti (co-PI), Carlotta Sacerdote (Coordinator). University of California, Irvine (USA): Hoda Anton-Culver (PI), Nancy Leighton (Coordinator). University of Michigan, Ann Arbor (USA): Stephen Gruber (PI, currently at USC Norris Comprehensive Cancer Center), Joanne Jeter (Coordinator). New Jersey Department of Health and Senior Services, Trenton (USA): Judith Klotz (PI), Homer Wilcox (Co-PI), Helen Weiss (Coordinator). University of North Carolina, Chapel Hill (USA): Robert Millikan (PI - deceased), Nancy Thomas (Co-PI), Dianne Mattingly (Coordinator), Jon Player (Laboratory Technician). University of Pennsylvania, Philadelphia, PA (USA): Timothy Rebbeck (PI), Peter Kanetsky (Co-Investigator), Amy Walker (Laboratory Manager), Saarene Panossian (Laboratory Technician).

Funding/support: This work was supported by the National Cancer Institute at the National Institutes of Health grant numbers R01 CA112243, R01 112524, R01 CA112243-05S1, R01 CA112524-05S2, U01 CA83180, K05 CA CA 131675-02 and ES014635; and Michael Smith Foundation for Health Research Infrastructure Award to R.P.G.

Role of the sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; in the preparation of the manuscript; or in the review or approval of the manuscript.

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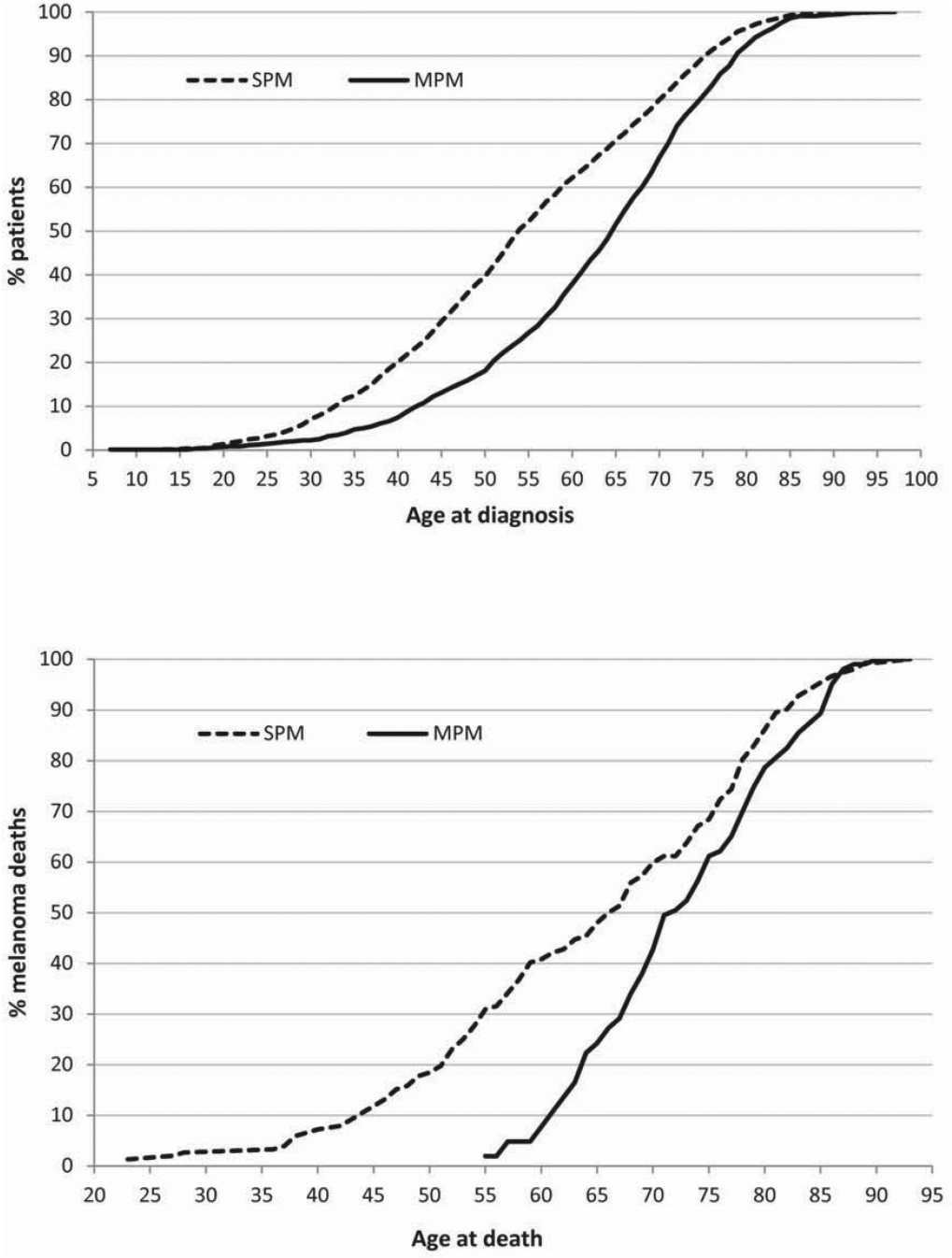

Figure 1.
Cumulative percentage distributions of cases by age at diagnosis (SPM) or at diagnosis of the selected lesion (MPM) and of melanoma deaths by age at death in 2372 SPM (152 melanoma deaths) and 1206 MPM (103 deaths) GEM patients.

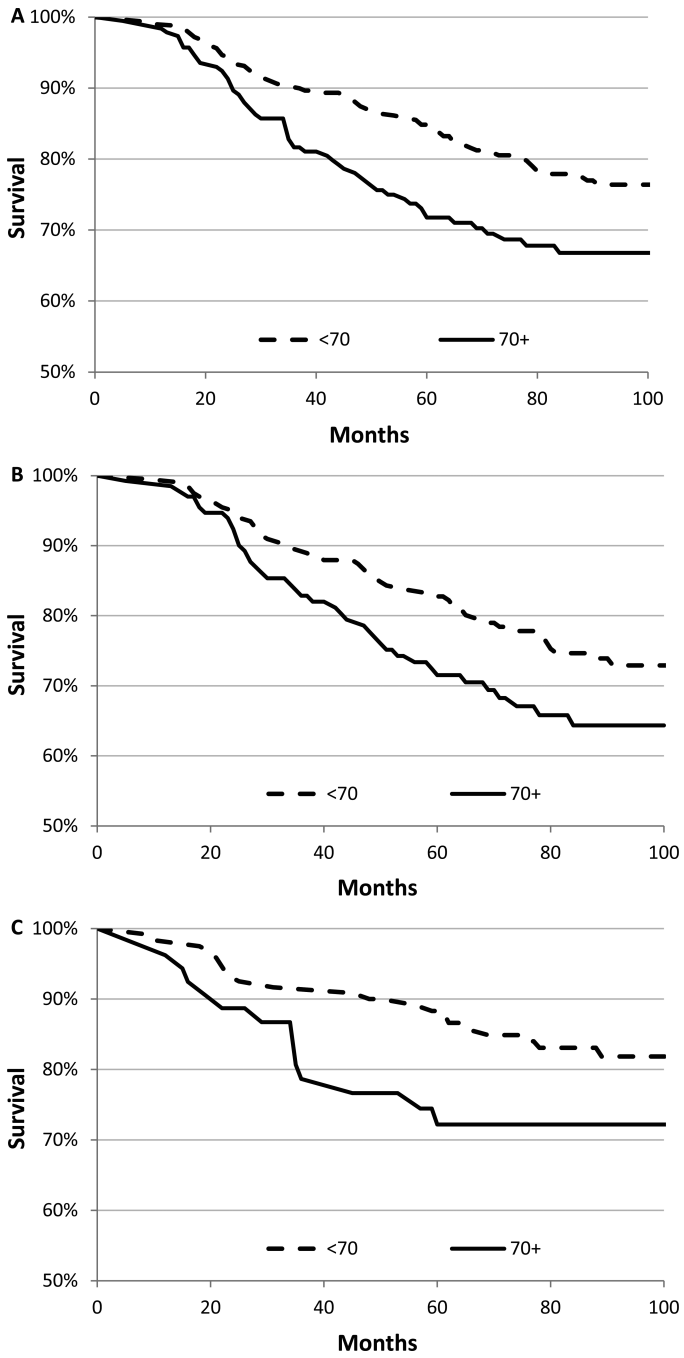

Figure 2.
Kaplan-Meier survival curves showing melanoma-specific survival for >2mm melanomas diagnosed at <70 or 70+ years of age in (A) men and women combined, (B) men, (C) women.

Table 1

Hazard ratios for melanoma death associated with status as SPM or MPM, and age, sex and pathology characteristics.

Characteristic	Censored *N*=2561	Dead *N*=209	HR (95% CI)[a]	*P*
Status				
SPM	1788	126	1.0	
MPM	773	83	1.24 (0.91-1.69)	.18
Age at diagnosis (years)				
<40	383	12	0.44 (0.23-0.84)	
40-49	424	20	0.65 (0.38-1.11)	
50-59	554	35	0.78 (0.50-1.20)	
60-69	511	57	0.95 (0.65-1.38)	
70-79	532	62	1.0	
80+	157	23	0.97 (0.59-1.59)	.15
Sex				
Male	1411	149	1.0	
Female	1150	60	0.86 (0.62-1.20)	.38
Site				
Trunk	1140	90	1.0	
Scalp	60	21	2.25 (1.37-3.71)	
Other head and neck[b]	340	39	1.10 (0.74-1.63)	
Arms	466	31	0.74 (0.49-1.12)	
Legs	555	28	0.65 (0.41-1.02)	<.001
Thickness (mm)				
0.01-1.00	1724	40	1.0	
1.01-2.00	515	63	3.42 (2.18-5.37)	
2.01-4.00	230	68	5.65 (3.44-9.28)	
>4.00	92	38	7.68 (4.46-13.23)	<.001
Ulceration				
Absent	2366	142	1.0	
Present	195	67	1.70 (1.22-2.37)	.002
Mitosis				
Absent	1510	43	1.0	
Present	1051	166	1.64 (1.08-2.51)	.02

Abbreviations: SPM, single primary melanoma; MPM, multiple primary melanoma; HR, hazard ratio; CI, confidence interval.

Censored/melanoma deaths by center in 2770 patients: New South Wales (Australia) 1079/111; Tasmania (Australia) 105/11; British Columbia (Canada) 132/8; Ontario (Canada) 420/31; Turin (Piemonte, Italy) 62/8; California (Orange County and San Diego) 141/3; Michigan (USA) 263/21; New Jersey (USA) 104/8; and North Carolina (USA) 255/8.

[a]Adjusted for age (continuous), sex, center, family history, education and all other variables in the table; HRs for age were estimated in a model of age grouped by decade. Excludes patients with missing data, most commonly due to lack of information on ulceration or mitoses in melanomas for which pathology could not be reviewed (18% SPM, 32% MPM). A missing value indicator was used for family history. Time of origin for MPM is date of diagnosis and pathology variables for MPM are those of the selected MPM.

[b]Other head and neck includes ears, face, unspecified face, neck.

Table 2

Hazard ratios for melanoma death by American Joint Committee on Cancer (AJCC) melanoma tumor stage.

AJCC tumor stage		Censored *N*=3323	Dead *N*=255	HR (95% CI)[a]
T1a ≤1.0mm	a. no ulceration or mitoses	1346	25	1.0
T1b	b. ulceration or mitoses	390	15	2.09 (1.10-3.96)
T2a 1.01-2.0mm	a. without ulceration	460	52	5.45 (3.37-8.80)
T2b	b. with ulceration	58	13	9.48 (4.82-18.64)
T3a 2.01-4.0mm	a. without ulceration	152	37	10.87 (6.53-18.10)
T3b	b. with ulceration	81	31	15.30 (8.97-26.10)
T4a >4.0mm	a. without ulceration	53	17	12.96 (6.96-24.13)
T4b	b. with ulceration	39	23	23.00 (12.85-41.14)
Unknown		744	42	3.19 (1.89-5.41)
				P<.001

Abbreviations: SPM, single primary melanoma; MPM, multiple primary melanoma; HR, hazard ratio; CI, confidence interval, AJCC American Joint Committee on Cancer.

[a]Adjusted for age, sex, center, melanoma status (SPM or MPM), family history, education and site (5 level); time of origin for MPM is date of diagnosis and pathology variables are those of the selected MPM. Patients with missing data are included in the 'unknown' category', mostly for ulceration or mitoses in melanomas for which pathology could not be reviewed (18% SPM, 32% MPM). A missing value indicator was used for family history.