Gender Differences in Melanoma Survival: Female Patients Have a Decreased Risk of Metastasis

Arjen Joosse[1], Esther de Vries[1,5], Renate Eckel[2], Tamar Nijsten[3], Alexander M.M. Eggermont[4], Dieter Hölzel[2], Jan Willem W. Coebergh[1,5] and Jutta Engel[2], for the Munich Melanoma Group[6]

Female melanoma patients generally exhibit significantly longer survival than male patients. This population-based cohort study aimed to investigate gender differences in survival and disease progression across all stages of cutaneous melanoma. A total of 11,774 melanoma cases extracted from the Munich Cancer Registry (Germany), diagnosed between 1978 and September 2007, were eligible to enter the study. Hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for tumor and patient characteristics, were estimated for the end points of survival, regional and systemic progression, and survival after progression. A significant female advantage was observed for melanoma-specific survival (adjusted HR 0.62; 95% CI 0.56–0.70). Women were at a lower risk of progression (HR 0.68; 95% CI 0.62–0.75), including a lower risk of lymph node metastasis (HR 0.58; 95% CI 0.51–0.65) and visceral metastases (HR 0.56; 95% CI 0.49–0.65). They retained a significant survival advantage after first progression (HR 0.81; 95% CI 0.71–0.92) and lymph node metastasis (HR 0.80; 95% CI 0.66–0.96), but this became borderline significant (HR 0.88; 95% CI 0.76–1.03) after visceral metastasis. Localized melanomas in women had a lower propensity to metastasize, resulting in a better survival when compared with men, even after first disease progression. These results suggest differences in tumor–host interaction across gender.

Journal of Investigative Dermatology (2011) **131,** 719–726; doi:10.1038/jid.2010.354; published online 9 December 2010

INTRODUCTION

In 1967, Wallace H Clark (Clark *et al.*, 1969) noted that melanoma was more aggressive in males. Since then, numerous studies have consistently confirmed gender to be an independent prognostic factor after adjustment for, e.g., age, Breslow thickness, histological subtype, body site (Downing *et al.*, 2006; Lasithiotakis *et al.*, 2008; de Vries *et al.*, 2008), ulceration (Balch *et al.*, 2001b; Azzola *et al.*, 2003), vascular invasion (Nagore *et al.*, 2005), mitotic rate, Clark level (Azzola *et al.*, 2003), and sentinel lymph node positivity (Scoggins *et al.*, 2006; Lasithiotakis *et al.*, 2008). Hence, a biological basis was suggested to underlie this female survival advantage (Lasithiotakis *et al.*, 2008; de Vries *et al.*, 2008). Several investigators hypothesized female melanoma patients to be somehow protected against metastasis (Kemeny *et al.*, 1998; Nieto *et al.*, 2003; Daryanani *et al.*, 2005). However, the precise differences in metastatic patterns across gender remain unclear. Some have stated that gender influences only local cancer invasion (Molife *et al.*, 2001); others have hypothesized that the effect is limited to lymphogenous (Richardson *et al.*, 1999) or hematogenous (Scoggins *et al.*, 2006) metastasis. Given the conflicting results (Kemeny *et al.*, 1998; Balch *et al.*, 2001b; Hofmann *et al.*, 2007), it also remains controversial whether the superior female survival is restricted to early-stage melanoma or also pertains to patients diagnosed with metastatic disease.

This observational study assessed gender differences in several phases of melanoma progression and across all melanoma stages. We used data from the Munich Cancer Registry (MCR).

RESULTS

Study population

Of the total of 11,734 patients analyzed, 49.3% were male (Table 1). Between 1978 and 1992 most of the newly registered melanoma patients were female, but after 1992 there was a higher incidence of male patients. Men exhibited

[1]*Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands;* [2]*Munich Cancer Registry (MCR) of the Munich Cancer Center (MCC), Institute of Medical Informatics, Biometry and Epidemiology (IBE), Ludwig-Maximilians-University (LMU), Munich, Germany;* [3]*Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [4]*Department of Surgical Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center, Rotterdam, The Netherlands and* [5]*South Netherlands Cancer Registry, Comprehensive Cancer Centre South (IKZ), Eindhoven, The Netherlands*

[6]*Munich Melanoma Group: M Volkenandt, Clinic and Policlinic for Dermatology and Allergology of the Ludwig-Maximilians-University (LMU); J Ring and R Hein, Clinic and Policlinic for Dermatology and Allergology, ''am Biederstein'' of the Technical University Munich (TUM); W Stolz, Clinic for Dermatology, Allergology and Environmental Medicine, Hospital Munich-Schwabing, Munich, Germany*

Correspondence: Arjen Joosse, Department of Public Health, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: a.joosse@erasmusmc.nl

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; MCR, Munich Cancer Registry

Received 9 June 2010; revised 28 September 2010; accepted 17 October 2010; published online 9 December 2010

Table 1. Descriptive data of study population: newly diagnosed patients with cutaneous melanoma recorded in the MCR

	Males		Females		
	N	%	*N*	%	*P*-value
Total	5,779	49.3%	5,995	50.7%	
variable					
Patient characteristics					
Age					
Median (y)	58.5		55.9		
Mean (y)	57.2		55.9		<0.001
Year of MM diagnosis				Overall	*<0.001*
1978–1982	313	5.4%	438	7.4%	<0.001
1983–1987	610	10.6%	673	11.3%	0.20
1988–1992	922	16.0%	1,063	17.9%	0.01
1993–1997	1,059	18.3%	970	16.3%	<0.01
1998–2002	1,557	26.9%	1,475	24.8%	0.01
2003–2006	1,318	22.8%	1,336	22.4%	0.63
Primary tumor characteristics					
Breslow thickness					
Median (mm)	0.84		0.75		
Mean (mm)	1.81		1.70		0.23
In categories:				Overall	*<0.001*
<1.0 mm	2,942	50.9%	3,261	54.4%	<0.001
1.01–2.0 mm	1,003	17.4%	1,007	16.8%	0.52
2.01–4.0 mm	695	12.0%	560	9.3%	<0.001
>4.0 mm	415	7.2%	355	5.9%	0.01
Missing	724	12.5%	772	12.9%	0.48
Histology				Overall	*<0.001*
SSM	3,085	53.4%	3,091	51.9%	0.11
NM	1,313	22.7%	1,295	21.7%	0.21
LMM	377	6.5%	500	8.4%	<0.001
ALM	121	2.1%	216	3.6%	<0.001
Other/NOS	883	15.3%	853	14.3%	0.15
Site				Overall	*<0.001*
Head and neck	945	16.4%	881	14.8%	0.02
Trunk	2,503	43.3%	1,259	21.1%	<0.001
Upper extremity	1,301	22.5%	1,311	22.0%	0.52
Lower extremity	933	16.1%	2,431	40.8%	<0.001
NOS	97	1.7%	73	1.2%	0.04
Ulceration				Overall	*0.13*
No	1,896	32.8%	1,913	32.1%	0.09
Yes	267	4.6%	237	4.0%	0.43
Missing	3,616	62.6%	3,805	63.9%	0.14
TNM stage at diagnosis					
N stage at diagnosis				Overall	*<0.001*
N0/NX	5,481	94.8%	5,776	97.0%	
N1+	298	5.2%	179	3.0%	
M stage at diagnosis				Overall	*0.01*
M0	5,682	98.3%	5,891	98.9%	
M1	97	1.7%	64	1.1%	
Disease progression during follow-up					
Disease progression?				Overall	*<0.001*
Yes	1,257	21.8%	934	15.7%	
No	4,522	78.2%	5,021	84.3%	
Local recurrence?				Overall	*0.50*
Yes	266	4.6%	290	4.9%	
No	5,513	95.4%	5,665	95.1%	
In-transit/satellite metastasis?[1]				Overall	*0.10*
Yes	52	0.9%	72	1.2%	
No	5,727	99.1%	5,883	98.8%	
Lymph node metastasis?				Overall	*<0.001*
Yes	805	13.9%	516	8.7%	
No	4,979	86.1%	5,439	91.3%	
Distant metastasis?				Overall	*<0.001*
Visceral metastasis	675	11.7%	406	6.8%	<0.001
Distant skin/LN metastasis	274	4.7%	247	4.1%	0.13
No distant metastasis	4,830	83.6%	5,302	89.0%	<0.001

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; LN, lymph node; MCR, Munich Cancer Registry; MM, malignant melanoma; NM, nodular melanoma; NOS, not otherwise specified; SSM, superficial spreading melanoma; TNM stage, tumor–node–metastasis stage.
[1]Of the total of 124 in-transit/satellite metastases, *n*=119 were in-transit and *n*=5 were satellites.

a disadvantaged distribution for almost all prognostic indicators (Table 1), being significantly older at diagnosis, having thicker melanomas, and having more melanomas

Table 2. Survival after melanoma diagnosis: multivariable analysis comparing females with males

		Crude HR		Adjusted HR[2]			Fully adjusted HR[3]	
End point	Events (%)[1]	HR	95% CI	HR	95% CI	Included confounder(s)[2]	HR	95% CI
Overall survival								
Males	1,929 (33.3)	1.00	Ref	1.00	Ref	Breslow	1.00	Ref
Females	1,540 (25.7)	0.67	0.63–0.72	0.71	0.66–0.75		0.69	0.64–0.74
Melanoma-specific survival								
Males	851 (14.7)	1.00	Ref	1.00	Ref	Breslow	1.00	Ref
Females	547 (9.1)	0.55	0.50–0.62	0.59	0.53–0.66		0.62	0.56–0.70

Abbreviations: CI, confidence interval; HR, hazard ratio.
[1]Absolute numbers of deaths that were observed and the percentages within the male/female groups.
[2]The following confounders were tested: age, year of diagnosis (YOD), primary tumor Breslow thickness (in AJCC (American Joint Cancer Classification System) categories), histology and body site, and N-stage and M-stage at the time of diagnosis. If a confounder adjusted the male excessive risk of death by ⩾10%, it was considered an eligible confounder and was added to the adjusted Cox proportional hazards model.
[3]Adjusted for all confounders: age, year of diagnosis, primary tumor Breslow thickness, histology and localization, and N-stage and M-stage at the time of diagnosis.

localized on the trunk or head and neck. In analyses of histological subtypes, females had significantly more lentigo maligna melanomas and acral lentiginous melanomas, but the incidence of SSM and nodular melanoma did not differ across gender. Males more often presented with lymph node metastases or distant metastasis at diagnosis than did females (5.2 vs. 3.0% and 1.7 vs. 1.1%, respectively). Whereas overall disease progression, lymph node metastasis, and distant metastasis occurred significantly more often in males than in females, local recurrence and in-transit/satellite metastases were equally common. Median follow-up time of the total study population was 6.7 years (80 months).

Survival

Of the total 11,734 patients, 3,469 died during follow-up, including 1,398 registered melanoma deaths. The crude 10-year overall survival rate was 70% and considerably higher in females than in males (76 vs. 65%). Similarly, adjusted overall survival for females was much better than for males (adjusted hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.66–0.75; Table 2), which was even more pronounced in melanoma-specific survival (adjusted HR 0.59; 95% CI 0.53–0.66). Breslow thickness was the only confounder affecting the gender survival difference. Subgroup analyses showed that neither ulceration nor the proxy for menopausal status considerably affected survival differences across gender (data not shown). Comparing our survival plots according to stages I to IV with those of the American Joint Committee on Cancer (AJCC) 2001 classification validation resulted in an almost complete overlap. In the subgroup with known ulceration status, the presence of ulceration upstaged melanomas classified in Breslow thickness categories. The best prognosis in stage IV patients was observed for skin and distant lymph node metastases, followed by lung metastases; the poorest prognosis was for other visceral metastases. These observations are in accordance with AJCC validation studies.

Progression after localized melanoma diagnosis

Females were at a lower risk of disease progression as recorded at follow-up (adjusted HR 0.69; 95% CI 0.63–0.75; Table 3). No significant differences across gender were observed for local recurrence or in-transit/satellite metastases. However, the probability of progressing to stage III (lymph node metastasis) and stage IV (distant metastasis) was significantly lower in women as compared with men (adjusted HRs 0.58; 95% CI 0.51–0.65 and 0.64; 95% CI 0.57–0.71, respectively). Among distant metastasis subcategories, gender did not significantly affect the occurrence of skin metastases or distant lymph node metastasis. However, the progression to visceral metastases was highly influenced by gender (adjusted HR 0.53; 95% CI 0.46–0.61), with similar estimates for the occurrence of liver, lung, and brain metastases. Breslow thickness and primary tumor body site were the only confounders consistently included in the multivariable analyses. Subsequent full adjustment with all available confounders did not greatly affect gender estimates for disease progression (Table 3), nor did adjusting for ulceration or menopausal status in the subgroup analyses (data not shown).

Survival after melanoma progression

Out of 2,191 patients who progressed, 1,110 died from melanoma (Table 4). After first progression of disease, women retained a survival advantage of 16% as compared with males (adjusted HR 0.84; 95% CI 0.74–0.95). This advantage was also significant after in-transit/satellite and lymph node metastasis, but borderline significant for survival after local recurrence and distant metastasis. Overall, no significant adjusted gender effects were observed for survival after any of the subtypes of distant metastasis. However, the effect of gender on survival after visceral metastasis also approached significance (adjusted HR 0.87; 95% CI 0.74–1.01). Full adjustment for all available confounders did not considerably change the adjusted gender estimate. Owing to lack of

Table 3. Disease progression after melanoma diagnosis: multivariable disease-free survival analysis comparing females with males[1]

		Crude HR		Adjusted HR[3]			Fully adjusted HR[4]	
End point	Events (%)[2]	HR	95% CI	HR	95% CI	Included confounder(s)[3]	HR	95% CI
Any first melanoma recurrence	2,191 (18.7)	0.66	0.61–0.72	0.69	0.63–0.75	Breslow, body site	0.68	0.62–0.75
Local recurrence	476 (4.1)	0.95	0.80–1.14	0.86	0.71–1.03	All confounders were included	0.86	0.71–1.03
In-transit/satellite metastasis	124 (1.1)	1.28	0.90–1.83	0.92	0.63–1.34	YOD, Breslow, histology, body site	0.90	0.62–1.32
Lymph node metastasis	1,321 (11.3)	0.58	0.52–0.65	0.58	0.51–0.65	Breslow, body site	0.58	0.51–0.65
Distant metastasis	1,602 (13.7)	0.61	0.55–0.67	0.64	0.57–0.71	Breslow, body site	0.64	0.58–0.71
Distant skin metastasis	321 (2.7)	0.83	0.66–1.03	0.75	0.59–0.94	Breslow, histology, body site	0.74	0.59–0.94
Distant LN metastasis	200 (1.7)	0.76	0.58–1.01	0.67	0.50–0.90	Breslow, body site	0.68	0.51–0.92
NOS	182 (1.6)	0.75	0.56–1.00	0.82	0.61–1.09	Breslow	0.85	0.63–1.16
Visceral	899 (7.7)	0.50	0.43–0.57	0.53	0.46–0.61	Breslow	0.56	0.49–0.65
Liver	220 (1.9)	0.49	0.37–0.64	0.53	0.40–0.70	Breslow	0.54	0.40–0.72
Lung	344 (2.9)	0.44	0.36–0.57	0.47	0.40–0.60	Breslow	0.50	0.40–0.64
Brain	188 (1.6)	0.49	0.36–0.66	0.53	0.39–0.71	Breslow	0.58	0.42–0.79
Other visceral	147 (1.3)	0.66	0.48–0.92	0.73	0.52–1.03	Breslow, body site	0.74	0.53–1.05

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, lymph node; NOS, not otherwise specified; YOD, year of diagnosis.
[1]All HRs were calculated for females compared with males as reference category.
[2]Absolute number of events and the percentages of the total of 11,734 patients.
[3]The following confounders were tested: age, YOD, primary tumor Breslow thickness (in AJCC (American Joint Cancer Classification System) categories), histology, and body site. If a confounder adjusted the male excessive risk of death by $\geqslant 10\%$, it was considered an eligible confounder and was added to the adjusted Cox proportional hazards model.
[4]Adjusted for age, YOD, primary tumor Breslow thickness, histology, and body site.

power, subgroup analyses were not performed after disease progression.

DISCUSSION

Although the female melanoma survival advantage has been well established, there is little information on the gender effect on progression patterns. To our knowledge, this is the first study that not only analyzes gender survival differences but also simultaneously takes into account all types of melanoma progression. There have been speculations that gender might influence distinct phases of disease progression, namely, only local primary tumor invasion (Molife *et al.*, 2001), lymphogenous metastasis (Richardson *et al.*, 1999), or hematogenous metastasis (Scoggins *et al.*, 2006). However, we demonstrate that females are at a significantly lower risk of both lymph node and distant metastases when compared with males, even when adjusted for relevant prognostic factors. The largest gender difference was a $>50\%$ risk reduction of visceral (mostly liver, lung, and brain) metastases (Table 3). This lower risk for visceral metastases explains the largest part of the female survival advantage, as the gender HR for melanoma-specific survival after first diagnosis (HR 0.62; Table 2) decreases considerably after the occurrence of visceral metastasis (HR 0.88; Table 4). Even after lymph node metastasis, females remain at a lower risk for subsequent distant metastasis, as indicated by their persisting survival advantage. Our results confirm the hypothesis that melanoma cells in females are at lower risk of disseminating, overcoming circulation, and establishing metastases at any site (Kemeny *et al.*, 1998; Nieto *et al.*, 2003; Daryanani *et al.*, 2005). Importantly, male gender is also associated with rapid growth of the primary melanoma (Liu *et al.*, 2006; Tejera-Vaquerizo *et al.*, 2009), although this was linked to a higher proportion of nodular melanoma, which we did not observe among males (Table 1).

The female survival advantage may persist even after spread to visceral organs, as suggested by our finding of a borderline significant effect of gender (HR 0.88, 95% CI 0.76–1.03, Table 4). Unfortunately, this analysis in stage IV patients was limited by the small sample size and missing information on important confounders, i.e., tumor burden and performance score. A few studies using stage IV trial databases were able to adjust for these confounders, but they yielded conflicting results: one meta-analysis ($n=813$) did not reveal a significant effect of gender, but five of nine reviewed studies reported gender as a prognostic indicator (Unger *et al.*, 2001). Another meta-analysis ($n=1,278$) showed a positive effect of female gender on prognosis of patients with stage IV melanoma (HR 0.78; $P<0.0001$; Korn *et al.*, 2008). Female patients with brain metastases have also been reported to exhibit better survival (Hofmann *et al.*, 2007). On the basis of both our results and the literature, we believe that a small independent female survival advantage persists in stage IV that is significant when a study sample is large enough. According to our results, however, this might not be true for survival after liver metastasis (HR 1.06; Table 4).

Table 4. Survival after melanoma progression: multivariable analysis comparing females with males[1]

Disease progression[2]	Events/no. of patients[3]	(%)	Crude HR		Adjusted HR[4]		Included confounder(s)[4]	Fully adjusted HR[5]	
			HR	95% CI	HR	95% CI		HR	95% CI
Any first melanoma recurrence	1,110/2,191	50.7	0.75	0.66–0.84	0.84	0.74–0.95	Body site	0.81	0.71–0.92
Local recurrence	191/476	40.1	0.69	0.52–0.92	0.73	0.54–1.00	Age, Breslow, body site	0.77	0.56–1.05
In-transit/satellite metastasis	39/121	32.2	0.54	0.29–1.02	0.39	0.16–0.95	All confounders were eligible	0.39	0.19–0.95
Lymph node metastasis	552/1,321	42.8	0.77	0.65–0.92	0.82	0.68–0.99	Breslow, body site	0.80	0.66–0.96
Distant metastasis	1,005/1,602	62.7	0.78	0.69–0.89	0.90	0.78–1.03	Body site, site of metastasis[6]	0.89	0.78–1.03
Distant skin metastasis	162/321	50.5	0.79	0.58–1.07	0.84	0.60–1.17	Breslow, body site	0.82	0.58–1.16
Distant LN metastasis	91/200	45.5	0.96	0.63–1.45	1.08	0.67–1.74	All confounders were eligible	1.08	0.67–1.74
NOS	128/182	70.3	0.79	0.55–1.12	0.84	0.56–1.26	YOD, Breslow, histology	0.88	0.58–1.35
Visceral[7]	822/899	91.4	0.84	0.73–0.97	0.87	0.74–1.01	Body site	0.88	0.76–1.03
Liver[7]	206/220	93.6	1.01	0.76–1.35	1.06	0.76–1.48	All confounders were eligible	1.06	0.76–1.48
Lung[7]	311/344	90.4	0.84	0.66–1.07	0.80	0.63–1.02	YOD, Breslow	0.84	0.65–1.09
Brain[7]	176/188	93.6	0.79	0.58–1.07	0.76	0.55–1.06	Age, histology, body site	0.78	0.56–1.09
Other visceral[7]	129/147	87.8	0.70	0.49–1.00	0.84	0.58–1.22	Age, YOD	0.85	0.58–1.25

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified; YOD, year of diagnosis.
[1]All HRs were calculated for females compared with males as reference category.
[2]Follow-up starts at disease progression, and ends at lost to follow-up, malignant melanoma–specific death, or death from other causes. Hazard ratios across gender are calculated for melanoma-specific death (= the event), except for distant visceral metastasis, where HRs for overall survival (death of all causes) were calculated.
[3]No. of observed deaths/no. of patients with disease progression.
[4]The following confounders were tested: age as continuous variable, YOD as continuous variable, primary tumor Breslow thickness (in AJCC (American Joint Cancer Classification System) categories), histology, and body site. For ''first progression,'' the type of progression was also tested. For ''distant metastasis,'' ''distant metastasis (visceral/NOS),'' and ''visceral metastasis,'' a variable containing the subdivision of sites of these metastases was also tested. If a confounder adjusted the male excessive risk of death by $\geqslant$10%, it was considered an eligible confounder.
[5]Adjusted for age, YOD, primary tumor Breslow thickness, histology and body site, and site of metastasis (if applicable).
[6]Site of distant metastasis (in categories: skin/distant lymph node/visceral/NOS).
[7]Survival analysis was performed for the end point overall survival instead of melanoma-specific survival.

In summary, either a protective factor in females or a melanoma-stimulating factor in males seems to be responsible for an overall less aggressive course of the melanoma in females, and, although affecting progression throughout all melanoma stages, this gender factor seems to have the largest effect on the risk of visceral metastases.

It is known that males, as compared with females, are less likely to self-detect their melanomas (Liu *et al.*, 2006), have a lower awareness of skin cancer risk (Devos *et al.*, 2003), make fewer visits to health-care providers, and are less likely to engage in preventive behaviors (Courtenay, 2000). This results in diagnostic delays in males that probably explain their thicker tumors, older age, and higher AJCC stage at diagnosis, as observed in our population (Table 1) and consistently reported throughout the literature (Lasithiotakis *et al.*, 2008; de Vries *et al.*, 2008). These differences in detection might also explain the known gender differences in body-site distribution, i.e., more truncal melanomas in males and limb melanomas in females (Table 1; de Vries *et al.*, 2008; Kemeny *et al.*, 1998). Gender differences in survival have long been thought to result from these differences in detection. Our results, using the bivariate approach with the ''10% rule,'' indeed indicate that Breslow thickness and body site considerably influenced the gender effect (Tables 2–4), reflecting these differences in detection. However, gender remains an independent prognostic indicator after adjustment for these factors. Therefore, we conclude that the female survival advantage is independent of gender differences in detection or diagnostic delay. Another argument for this conclusion can be found in a comparison of regions worldwide. Although male/female incidence ratios differ greatly across continents, the female survival advantage has been very consistently reported in Europe (Leiter *et al.*, 2004; Downing *et al.*, 2006; Lasithiotakis *et al.*, 2008; de Vries *et al.*, 2008), Australia (Azzola *et al.*, 2003), and the United States (Kemeny *et al.*, 1998; Balch *et al.*, 2001b; Scoggins *et al.*, 2006). Therefore, incidence patterns are unlikely to explain the female survival advantage.

Other proposed explanations for the gender difference in melanoma survival include differences in the distribution confounders, such as age and ulceration; influence of estrogen in females; and the overall longevity of women. However, all other confounders—including age and ulceration and inclusion of menopausal age groups in the subgroup analyses—did not considerably change the gender estimates for survival or progression and therefore do not seem to contribute to the explanation of this phenomenon. Regarding menopausal status, this is consistent with recent conclusions that estrogens do not seem to affect melanoma (Gupta and Driscoll, 2010). Finally, given that the effect of

gender was more pronounced in melanoma-specific survival than in overall survival, the overall superior longevity of women is unlikely to explain their survival advantage in melanoma.

A major strength of our study is that we used a large population-based cancer registry that uniquely recorded different types of disease progression during follow-up through a meticulously refined system of follow-up. Illustrating the accuracy and validity of the MCR, the survival rates and effect of known confounders on survival within the registry highly resembled the results of the AJCC validation studies (Balch *et al.*, 2001a, 2001b).

Our study is limited by a lack of information on some confounders, including sentinel node biopsy and, for a large group of patients, ulceration. However, for the analyses with the subgroup with known ulceration status, survival curves were very similar to those in the AJCC 2001 validation study (Balch *et al.*, 2001b), bolstering their validity. Furthermore, we did not have information concerning mitotic rate of the primary, number of involved lymph nodes, and lymph node tumor burden, which are all included in the latest AJCC staging system (Balch *et al.*, 2009). The 30% of all melanoma-specific deaths without a distant metastasis registered during follow-up suggests a 30% rate of underreporting of metastasis. However, this is common in melanoma and unlikely to be associated with gender (i.e., a nondifferential misclassification bias).

Although the female advantage is consistently significant, the effect on prognosis is modest. For example, the 10% difference across gender for 10-year overall survival is small compared with the 50% higher survival rate for thin versus thick melanomas (<1 mm and >4 mm; 10-year survival rates 84 vs. 34%). Illustratively, Balch *et al.* (2001b) ranked gender as the sixth most important prognostic indicator. However, the gender effect is intriguing because it is so consistent and the cause remains unknown. To date, only one hypothesis has been published proposing that reactive oxygen species underlie this phenomenon (Joosse *et al.*, 2010).

MATERIALS AND METHODS

Setting

The MCR has been registering incident cancers in Munich since 1978, gradually extending to the surrounding region of Bavaria (3.8 million inhabitants), becoming population based in 1988. Incidence and primary tumor information (i.e., tumor–lymph node–metastasis (TNM) stage and histological tumor characteristics) are ascertained through pathology laboratories. Furthermore, clinicians complete standardized forms concerning patient characteristics, tumor diagnosis, TNM stage, information about therapy, and follow-up. Vital status is recorded by physicians and validated by yearly checks with the Bavarian registry of death certificates and the municipal registration offices.

Case ascertainment and available data

All melanomas diagnosed between 1978 and 2008 were extracted from the MCR database ($n=15,859$). The last complete check of vital status was performed on 20 September 2007; hence, melanoma cases diagnosed after 20 September 2006 were excluded so that information on at least 1 year of follow-up would be available for all patients. For patients with multiple melanomas, only the first invasive melanoma was used as the starting point of follow-up. *In situ* melanoma, lentigo maligna, noncutaneous melanoma, unknown primaries, and patients without follow-up were excluded (Table 5). For all eligible cases ($n=11,734$), date of diagnosis, patient characteristics, primary tumor characteristics, last known vital status, and cause of death were available. During follow-up, the occurrence of first progression (if any) and four distinct types of disease progression (local recurrence, in-transit/satellite metastasis, lymph node metastasis, and distant metastasis) were recorded (Table 1). Distant metastasis was subcategorized into visceral (i.e., lung, liver, brain, and other organs), distant skin, distant lymph nodes, and ''not otherwise specified'' metastasis. Because the diagnosis date was available only for the first distant metastasis diagnosed (marking progression to stage IV), subgroup analyses using the sites of distant metastasis (e.g., liver and lung) were based on the first distant metastasis only. Variables indicating the time from diagnosis to progression were calculated for all types of disease progression, and were coded ''0'' if patients presented with metastasis at the time of diagnosis. Death due to melanoma was defined using information obtained from the death certificate or from the clinics, or if a distant melanoma metastasis was recorded prior to death of unknown cause.

Table 5. Exclusion of patients with melanoma recorded in the MCR 1978–2008

	Number of melanomas	%
Total melanoma patients	15,859	100
Exclusion criteria		
Diagnosis after 20 September 2006	1,128	7.1
In situ melanoma[1]	1,969	12.4
Non-skin melanoma[2]	129	0.8
Unknown primary[3]	312	2.0
Assumed unknown primary[4]	154	1.0
Multiple melanomas[5]	432	2.7
No follow-up available	1	<0.0
Included patients	11,734	74.0

Abbreviation: MCR, Munich Cancer Registry.
[1]Coded as *in situ* in TNM stage variable or coded as ''*in situ* melanoma,'' ''lentigo maligna,'' or ''nevus'' in the histological classification variable.
[2]Coded as mucosal or genital melanoma in body site classification.
[3]Coded ''unknown primary,'' or as a visceral primary location in the body site classification.
[4]When no data were available for all of the following variables: TNM T-stage, Breslow thickness, body site, and histological subtype, the melanoma was excluded, and was assumed to be an unknown primary.
[5]The second and any subsequent primary melanomas of one patient extracted from the registry were excluded; i.e., only the first invasive melanoma was included.

Statistical analysis

We used χ^2 and Student's *t*-test to compare categorical and continuous variables, respectively. Kaplan–Meier tables were used

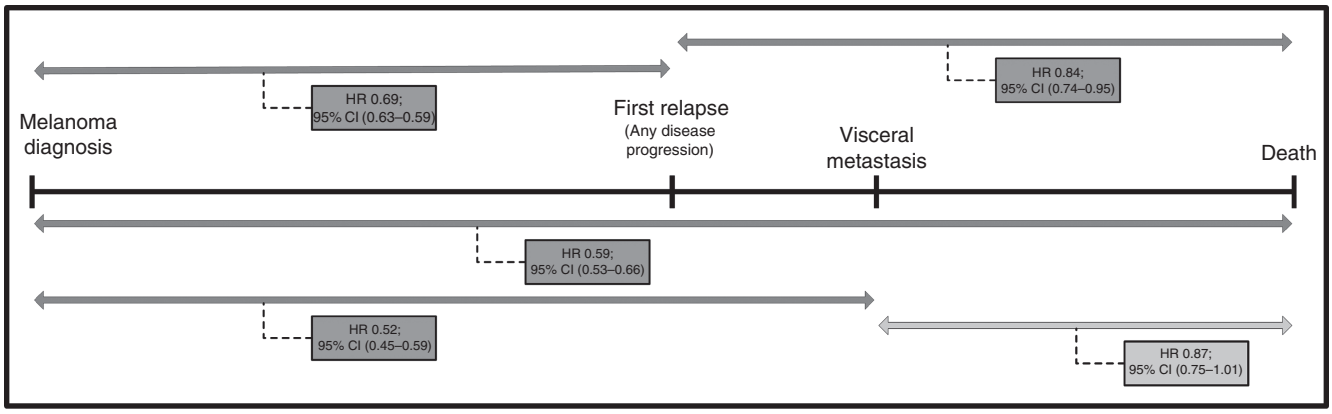

Figure 1. The female advantage in survival as well as before and after first progression and visceral metastasis. Hazard ratios for females as compared with males, presented in several time periods of melanoma progression related to diagnosis, disease recurrence, visceral metastasis, and death. Lighter gray represents borderline significance; darker gray represents significance as compared with males. CI, confidence interval; HR, hazard ratio.

to calculate crude 10-year overall survival rates. Cox regression models were used to calculate crude and adjusted HRs and 95% CIs for females compared with males, censoring cases that were lost to follow-up and, if applicable, cases with a non-melanoma-related cause of death. These survival analyses were performed separately for different phases in melanoma disease progression: (i) from diagnosis to overall or melanoma-specific death, (ii) from diagnosis to different end points of disease progression, and (iii) from diagnosis of disease progression to melanoma-specific death. For survival between visceral metastases and death, overall survival instead of melanoma-specific death was used as an end point to increase power, assuming that virtually all patients diagnosed with visceral metastases ultimately die of melanoma. The proportional-hazard assumption was checked by plotting log-minus-log plots for all confounders in all analyses, followed, if necessary, by landmark analysis to check the extent of nonproportionality (Harrell, 2001). This yielded one minor violation: gender effect showed some variation over time in log-minus-log plots, but only in the analysis concerning overall survival. Landmark analysis revealed that the effect of gender on overall survival was most profound in the early years after diagnosis (HR 0.60 for 0–4 years after diagnosis) and decreased significantly over time (HR 0.78 for >4–20 years after diagnosis, data not shown). For all other analyses, the proportional-hazard assumption was not violated. All statistical tests were two-sided. *P*-values <0.05 were considered significant. Statistical analysis was performed using SPSS 15.0.0 (SPSS, Chicago, IL).

Confounders

Available confounders for melanoma progression included age (continuous variable), year of diagnosis (continuous variable), Breslow thickness categorized according to the AJCC 2002 staging system (Balch *et al.*, 2001a), histological subtype, primary tumor body site, N and M classification at the time of diagnosis, and—after disease progression—the type of progression or site of distant (visceral) metastasis. For categorical variables, categories are described in Table 1. As recommended by the STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) guidelines for reporting of epidemiological studies (Vandenbroucke *et al.*, 2007), and to determine which confounders influence the gender difference, all available and appropriate confounders for each survival analysis were first separately tested in bivariate Cox models along with gender. If a confounder adjusted the HR of gender by $\geqslant 10\%$, it was included in the multivariable Cox regression model. To confirm that the nonincluded confounders indeed did not influence the gender estimate, a second multivariable "fully adjusted" model was performed, adjusting for all available confounders.

Ulceration of the primary tumor, which is an important factor in the current AJCC staging system (Balch *et al.*, 2001a), was excluded from our main analyses, as it was unknown for 63% of cases, especially in the earlier years of the study. However, subgroup analyses using only patients with known ulceration status ($n=4,313$) were performed to explore the effect of this important prognostic indicator on melanoma gender differences. Furthermore, to explore the potential influence of menopause, subgroup analyses were performed adjusting the gender estimate for a proxy of female menopausal status using age at diagnosis: premenopausal was defined as $\leqslant 45$ years old ($n=3,239$), menopausal as >45 and <60 years old ($n=3,312$), and postmenopausal as $\geqslant 60$ years old ($n=5,183$).

To validate the MCR database and the influence on survival of important prognostic factors included in the AJCC staging system, survival plots of all MCR cases stratified by stage I through IV were compared with those published by the AJCC melanoma group (Balch *et al.*, 2001a, b). This was repeated for survival plots stratifying for AJCC substages according to ulceration—if available—in stages I and II (IA–IIC) and site of metastasis in stage IV (M1–M3). Unfortunately, stage III patients could not be substaged because of missing information on the number of positive lymph nodes.

This cohort study is reported according to the STROBE guidelines (Vandenbroucke *et al.*, 2007).

CONCLUSION

In our population-based study, gender independently affected melanoma in all progression phases, reflected mainly in a reduced risk in females of visceral metastases (Figure 1), resulting in a significantly higher survival rate in females as compared with males. These results suggest a biological difference across gender in the disease and/or in the disease–host interaction. Research aimed at unraveling the underlying mechanisms may be of therapeutic relevance.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge Professor EW Steyerberg and Statistician BE Hansen from the Erasmus University Medical Center Departments of Public Health and Biostatistics, respectively, for the helpful discussions on survival analyses methodology.

REFERENCES

Azzola MF, Shaw HM, Thompson JF *et al.* (2003) Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. *Cancer* 97:1488–98

Balch CM, Buzaid AC, Soong SJ *et al.* (2001a) Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 19:3635–48

Balch CM, Gershenwald JE, Soong SJ *et al.* (2009) Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 27: 6199–206

Balch CM, Soong SJ, Gershenwald JE *et al.* (2001b) Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 19: 3622–34

Clark WH Jr, From L, Bernardino EA *et al.* (1969) The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 29:705–27

Courtenay WH (2000) Constructions of masculinity and their influence on men's well-being: a theory of gender and health. *Soc Sci Med* 50:1385–401

Daryanani D, Plukker JT, de Jong MA *et al.* (2005) Increased incidence of brain metastases in cutaneous head and neck melanoma. *Melanoma Res* 15:119–24

de Vries E, Nijsten TE, Visser O *et al.* (2008) Superior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. *Ann Oncol* 19:583–9

Devos SA, Baeyens K, Van Hecke L (2003) Sunscreen use and skin protection behavior on the Belgian beach. *Int J Dermatol* 42:352–6

Downing A, Newton-Bishop JA, Forman D (2006) Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993–2003. *Br J Cancer* 95:91–5

Gupta A, Driscoll MS (2010) Do hormones influence melanoma? Facts and controversies. *Clin Dermatol* 28:287–92

Harrell FEJ (2001) *Regression Modeling Strategies*. Springer: New York

Hofmann MA, Coll SH, Kuchler I *et al.* (2007) Prognostic factors and impact of treatment in melanoma brain metastases: better prognosis for women? *Dermatology* 215:10–6

Joosse A, De Vries E, van Eijck CH *et al.* (2010) Reactive oxygen species and melanoma: an explanation for gender differences in survival? *Pigment Cell Melanoma Res* 23:352–64

Kemeny MM, Busch E, Stewart AK *et al.* (1998) Superior survival of young women with malignant melanoma. *Am J Surg* 175:437–44

Korn EL, Liu PY, Lee SJ *et al.* (2008) Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 26:527–34

Lasithiotakis K, Leiter U, Meier F *et al.* (2008) Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer* 112:1795–804

Leiter U, Buettner PG, Eigentler TK *et al.* (2004) Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the German Dermatological Society. *J Clin Oncol* 22:3660–7

Liu W, Dowling JP, Murray WK *et al.* (2006) Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Arch Dermatol* 142:1551–8

Molife R, Lorigan P, MacNeil S (2001) Gender and survival in malignant tumours. *Cancer Treat Rev* 27:201–9

Nagore E, Oliver V, Botella-Estrada R *et al.* (2005) Prognostic factors in localized invasive cutaneous melanoma: high value of mitotic rate, vascular invasion and microscopic satellitosis. *Melanoma Res* 15:169–77

Nieto A, Ruiz-Ramos M, Abdel-Kader L *et al.* (2003) Gender differences in rising trends in cutaneous malignant melanoma in Spain, 1975–98. *Br J Dermatol* 148:110–6

Richardson B, Price A, Wagner M *et al.* (1999) Investigation of female survival benefit in metastatic melanoma. *Br J Cancer* 80:2025–33

Scoggins CR, Ross MI, Reintgen DS *et al.* (2006) Gender-related differences in outcome for melanoma patients. *Ann Surg* 243:693–8

Tejera-Vaquerizo A, Barrera-Vigo MV, Lopez-Navarro N *et al.* (2009) Growth rate as a prognostic factor in localized invasive cutaneous melanoma. *J Eur Acad Dermatol Venereol* 24:147–54

Unger JM, Flaherty LE, Liu PY *et al.* (2001) Gender and other survival predictors in patients with metastatic melanoma on Southwest Oncology Group trials. *Cancer* 91:1148–55

Vandenbroucke JP, von Elm E, Altman DG *et al.* (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 18:805–35