Superior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site.

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Abstract: (199 words)

Background: Worldwide, female melanoma patients have superior survival compared to males, which is usually ascribed to earlier detection among women and/or a more favourable site distribution. We studied gender difference melanoma survival in a large population-based setting after adjusting for tumor-related variables and offer clues for further research. Patients and Methods: A total of 10,538 patients diagnosed with melanoma between 1993 and 2004 in the Netherlands were included. Multivariate analyses were performed to estimate adjusted relative excess risk (RER) of dying for men compared to women, adjusted for the patient and tumour characteristics.

Results: Univariate relative survival analyses showed a RER of dying of 2.70 (95% CI 2.38 – 3.06) for men compared to women. After adjusting for time period of diagnosis, region, age, breslow thickness, histologic subtype, body site, nodal and metastatic status, a significant excess mortality risk was still present for males (RER 1.87, 95% CI 1.65-2.10). Mong patients with advanced disease and in those <45 or ≥60 the adjusted risk estimates were similar.

Conclusions: The superior survival of women compared to men persisted after adjusting for multiple confounding variables suggesting that factors other than stage at diagnosis and body site reduce mortality risk in female melanoma patients.

Introduction

Over the last decades, cutaneous malignant melanoma (melanoma) survival has improved in absence of major changes in treatment of advanced disease. The most important predictors of mortality, included in the AJCC staging, are tumor characteristics such as Breslow thickness, Clark level and ulceration, and nodal and visceral metastatic involvement [1]. Melanoma survival may have improved due to higher awareness, reduction of exposure to risk factors, early diagnosis and screening [2, 3].

In addition to tumor related factors, other variables may affect melanoma mortality. A number of epidemiologic studies have reported gender differences in both the occurrence and survival of melanoma [4-6]. In European countries, melanomas occur more often among females than males, but in other predominantly Caucasian populations such as Australia and the United States this malignancy is more common among males [7-9]. Unlike incidence rates, melanoma survival rates have worldwilde observed to be superior for women compared to men [4, 6]. The better female survival rate is assumed to be related to earlier diagnosis (i.e., thinner melanoma without lymph node involvement and/or metastatic spread) and the fact that melanomas in females often present on the extremities [10]. The latter site is associated with a better survival, which may be due to an easier clinical follow-up of lymph node involvement. Several (nested) cohort studies have adjusted for the most pivotal tumor characteristics and showed conflicting results about the causes of a gender difference in melanoma survival (Table 1)[5, 11-17].

Therefore, we investigated the gender difference in melanoma survival after adjusting for tumor related variables in a large population-based setting using three Dutch

population-based cancer registries. Increasing the understanding of gender differences in survival of melanoma patients may improve care of melanoma patients such as staging and follow up. Also, this may stimulate additional research in order to explain a possible observed difference, which may result in new treatment options.

Methods

In this study, data from the Comprehensive Cancer Centres Amsterdam (IKA), North (IKN) and South (IKZ) (http://www.ikcnet.nl) were used. These Comprehensive Cancer Centres host cancer registries, which collect data on all patients with newly diagnosed cancer in their respective regions. Together, these registries serve a population of ±7 (IKZ 2.4, IKA 3.0, IKN 1.6) million inhabitants (± 44% of the entire Dutch population).

All incident melanoma cases diagnosed in these regions between 1993 (IKZ) / 1994 (IKN, IKA) and 2004 (n=10,538) with more than 1 day of follow-up (n=55 cases had 1 day or less follow-up) were included for analysis and followed up until February 2006, resulting in 59,914 person-years of follow-up.

Data on vital status were obtained from the hospital records and the municipal civil registries. During the period of observation, a total of 2584 (24%) of the included melanoma patients died.

Five year relative survival rates were calculated. Relative survival is an estimation of disease-specific survival. It is calculated as the absolute survival rate among cancer patients divided by the expected survival rate in the period of diagnosis from the general population with the same sex and age structure [4, 18]. We performed multivariate relative survival analyses [19] by the known prognostic factors that were available from the cancer registry such as age at diagnosis, sex, body site, histological subtype, Breslow thickness, nodal involvement and absence or presence of metastasis. Body site was subdivided into head and neck, arms, trunk, legs and unknown body site. Histological subtype was divided into superficial spreading melanomas (SSM), nodular melanomas (NM), lentigo maligna melanomas (LMM),

acral lentiginous melanomas (ALM) and other melanomas (other), which included all other types of melanomas and melanomas of which histogenetic subtype was unknown. We made a subdivision into melanomas with a Breslow thickness thinner than 1.0 mm, between 1.01 and 2.0 mm, 2.01-4.0 mm and more than 4.0 mm according to the AJCC staging system[1]. In the multivariate model, the abovementioned confounding variables and pre-specified interaction terms (i.e., nodal status*metastatic status, nodal status*Breslow thickness, period*Breslow thickness, agegroup*sex, sex*body site, sex*Breslow thickness, period*breslow thickness, region*nodal status and region*metastatic status) were included. Following a backward procedure, excluding the least significant interactions (cut-off p-value: 0.1), variables and interactions were removed from the model in the following order: agegroup*sex (p=0.83), period*breslow thickness (p=0.72), period (p=0.59), nodal status*region (p=0.33), metastatic status*region (p=0.21), sex&body site (p=0.22), sex*breslow (p=0.24).

For the patients diagnosed in the period 2003/2004, information on ulceration was present, and analyses were also performed for this subgroup of patients.

In addition to the primary survival analysis, several sub-analyses were performed to study the impact of gender on melanoma progression. First, the effect of gender on melanoma survival among patients with advanced disease (defined as patients with reported lymphnode and/or systemic involvement) was assessed using a multivariate model that adjusted for pre-specified prognostic factors (i.e, age, sex, breslow thickness and body site) in this nested cohort. Secondly we studied wether the gender difference was only present during the first years after diagnosis or wether it persisted also on the long run.

To assess whether endogenous female hormones are important in the possible difference between men and women, we repeated the same analyses for cases who were <45 and ≥60 years old and excluded those between 45 and 60 years old. In addition, we analysed the effect of menopausal status among women only.

All analyses were performed using the SAS computer package (SAS Institute Inc., Cary, North Carolina, USA, 1999), using a publicly available macro: http://www.pauldickman.com/rsmodel.

Results

Study population

Of the 10,538 cases, 57.9% were female and the mean age was 54.04 years (Table 2). All included tumour characteristics were less favourably distributed among male compared to the female patients: males were significantly older and more likely to have nodular melanoma, truncal and head and neck melanoma, higher Breslow thickness and nodal or visceral involvement.

Univariate analyses of gender difference in melanoma survival

The five-year relative survival was higher for women (89%, 95% CI 88%-90%) than for men (76%, 95% CI 75%-78%). Corresponding crude survival rates were 82% for women and 68% for males. Both crude (Kaplan-Meier) and relative survival analyses showed a significant gender difference in survival (Log-rank test χ^2 279.1, df=1, $p<0.0001$; RER males vs females 2.70 (95% CI 2.38-3.06))(Figure 1; Table 3).

Multivariate analyses of gender difference in melanoma survival

After adjusting for region, age, Breslow thickness, histologic subtype, body site, nodal and metastatic status and interaction terms, excess mortality risk for males compared to females decreased from 2.7 to 1.87 (95% CI 1.65-2.10). In the multivariate model, Breslow thickness, histology, body site, nodal involvement and metastatic spread remained important predictors of melanoma associated mortality (Table 3). There were also differences in melanoma survival by region, the reasons for which remain unclear.

Multivariate analyses of gender difference among patients with information on ulceration (diagnosed in 2003/2004)

Of all patients diagnosed in 2003-2004 (n=773), 115 had ulceration (15%), 523 did not show ulceration and of 135 patients no information on ulceration was available (table 2). The results of the multivariate analyses including age, sex, breslow thickness, TNM stage, breslow and ulceration still show a RER of 1.5 although this did not reach significance (table 4).

Multivariate sub-analyses of gender difference in melanoma survival

Of the 10,538 cases, 534 individuals (5.1%) had pathology confirmed advanced disease (TNM-N+/M+). In a multivariate model among these advanced cases, adjusting for age, body-site and Breslow thickness, the superior female survival persisted (male RER 1.70, 95%CI 1.30-2.23 compared to women).

Over time, the risk estimates remained in favor of women. After 5 years of follow-up the adjusted survival difference between men and women was no longer significant (table 5).

Stratifying by age resulted for those diagnosed with melanoma under the age of 45 (n=3386) in an adjusted RER of 1.74 (95% CI 1.35-2.25) for men compared to women, for those aged 60 year or older (n=3920) at diagnosis this was 1.86 (95% CI 1.44-2.39) after adjusting for region, age, period of diagnosis, Breslow thickness, histologic subtype, body site, nodal and metastatic status. Comparing premenopausal (age $\leq$ 45) with postmenopausal women ($\geq$60 years), adjusting for the same variables, the RER for pre—menopausal (young) women was 1.75 (95% CI 1.15-2.66) compared to the postmenopausal women.

Discussion

In this large population-based study, male melanoma patients were almost twice as likely to die compared to female patients. Although men were significantly more likely to have melanomas with unfavorable characteristics such as thicker and nodular melanomas located on the trunk, which is in accordance with previous observations [4, 20], adjusting for these factors did not fully explain the observed gender difference in melanoma survival. Although studies should be compared with caution because of the different study designs and populations, the protective effect of being female is in accordance with other large studies (Table 1). The strength of the risk estimate assessing gender difference is comparable to other well known risk factors such as ulceration, thickness, elderly age, tumor site and histological type (relative risks ±1.2-2.0)[4, 6, 16] emphasizing its importance.

Although the most common explanation for the gender difference in melanoma survival is the better stage at diagnosis among women, our results suggest that superior female survival is only partly explained by this phenomenon. After correcting for age, period of diagnosis, body site, Breslow thickness, nodal involvement and metastatic status, males were at a 1.9 times higher risk of dying from their melanoma compared to females. Recently, the assumption that Breslow thickness is a surrogate marker for the time between development and diagnosis of melanoma, which has been applied in many epidemiological studies, has been challenged. A large epidemiological study showed no positive association between melanoma thickness and time to diagnosis on a population basis and a histological study concluded that aggressive tumor growth, rather than delay in diagnosis, is responsible for the development of thick melanoma.[21, 22] More aggressive melanoma growth, not

included in this analysis, appears to occur more often in elderly men and may explain the better female survival [21, 22].

Prognostic factors like mitotic rate may be included in future classifications and subsequently registered in population-based cancer registries. Future studies on the superior female survival of melanoma may then include this variable as an important confounder. Specialised melanoma registries may contain information on molecular pathological variables and such databases could shed light on the possible mechanisms behind the gender differences in melanoma survival.

In our study, there was only a small proportion of patients with positive lymph nodes. This partly reflects the relative early detection of melanomas in the Netherlands, but is also caused by the low rate of sentinel node procedures in our country in the past, but also in more recent years. The most recent clinical guideline for melanoma states that ”this procedure is only reserved for patients who wish to be very accurately informed with regards to their prognosis”, and that “the sentinel node procedure is not part of the standard diagnostic procedures for melanoma patients” [23].

Some important melanoma characteristics such as ulceration, which appears to be a marker for dysregulation of the DNA replication system that is related to melanoma progression, were only available for patients diagnosed in 2003 and 2004 (N=773). Due to the small numbers of patients and few deaths (N=79) in the short follow-up period that was available, no firm conclusions can be drawn from these sub-analyses. The importance of tumor ulceration is illustrated by the fact that both studies that adjusted for tumor ulceration, showed no significant gender difference in melanoma survival (Table 1)[11, 14]. We observed an increased risk of death for

males, but this was no longer significant. However, this could be due to a lack of power and the short follow-up time (maximum 3 years) for this subset of patients.

A few earlier studies suggested an increased melanoma risk in (long-term) oral contraceptive use [24, 25], but metanalyses did not confirm this association [26, 27]. In randomized clinical trials, tamoxifen did not improve the survival rate in patients with metastatic melanoma [28]. The likelihood of developing melanoma and its prognosis were comparable in pregnant and non-pregnant females [28, 29] and a recent case control study that focused on melanoma in women did not find reproductive, menstrual and hormonal factors that affected melanoma risk [29]. In our study, the superior survival of women was apparent in both the pre- and postmenopausal age groups, implying that estrogens did not substantially influence the observed survival difference. Moreover, pre-menopausal women diagnosed with a melanoma had an increased relative excess risk of death compared to post-menopausal women, after adjusting for age and other prognostic factors. In contrast with these epidemiological and clinical findings, in vitro studies showed that tamoxifen and a derivative and 17-β-oestradiol significantly reduced melanoma cell invasion [30].

Multiple other factors, speculated to be possibly related to melanoma prognosis and possibly differently distributed among men and women, were not available in the Dutch population-based cancer registries. A gender difference in the prevalence of life style factors such as sun exposure [31] and dietary habits such as vitamin supplements including vitamin D, ethanol consumption, soy isoflavones, essential fatty acids and drug use may in part explain the difference in survival across gender [32-38].

Interestingly, the superior survival of melanoma that has been reported worldwide, has not been observed among patients with familial melanomas, nor among uveal melanoma patients.[39, 40]

An implication of the study findings is that in the assessment of factors with prognostic importance for melanoma the results should be stratified across gender in an attempt to explain the observed gender difference, but also to investigate whether risk factors behave differently across gender. For example, the association of alcohol consumption and melanoma remains controversial [32-34], but the one study that stratified across gender showed that ethanol intake was significantly associated with melanoma in men only [33]. Interestingly, alcohol intake affects individuals' immunity differently in men and women [36]. Other putative melanoma risk factors that have been studied separately for men and women and may differ across gender include diet [38], statin use [35] and anthropometric measures [37].

To assess whether gender affects the early or late stages of melanoma (local vs systemic progression, respectively), time since diagnosis and patients with metastasis were studied separately. A few years post-presentation, female survival was significantly higher but lost statistical significance 5 years after diagnosis, either because of real loss of the protective effects of female gender in time or reduced sample size. Our results indicate the latter, as the risk estimates decreased but remained in favor of women, but statistical significance was lost. Comparing the survival rates across gender in patients with pathology confirmed metastasis demonstrated that the female advantage persists among patients with advanced disease. This observation suggests that the (immunological) response to melanoma (metastases) may differ between genders, which would be in accordance with a

sexual dimorphism in the immune response in humans [41]. For instance, females produce more vigorous cellular and more vigorous humoral immune reactions, are more resistant to certain infections, and suffer a higher incidence of autoimmune diseases. A recent study on non-melanoma skin cancers in mice showed gender differences in tumor development to be influenced more by oxidative DNA damage and antioxidant capacities than by inflammatory responses[42]. Moreover, three-way interactions between sex hormones, inflammation and prostate and liver cancer have been discovered [43]. Basic science studies are warranted to investigate the possible difference in immunological response to melanoma between genders.

Compared to previous studies, we included at least twice as many cases, adjusted for three out of four tumor characteristics (Table 1) and calculated relative excess risk estimates. Because the vital status but not cause-of-death of each melanoma patient was known, relative survival rather than absolute survival rates were estimated [19]. This statistical technique provides insight into the ‘excess mortality’ that cancer patients suffer compared to the general population. In addition to the gender difference, we observed the expected associations for all variables included in the model. The risk of dying was higher for elderly patients and for those with a high Breslow thickness, nodular rather than superficial spreading melanomas, for truncal melanomas and melanomas with an unknown primary site, with nodal involvement and visceral metastasis. These expected findings suggest that the internal validity of the study is good. The completeness of the Dutch cancer registries has been demonstrated to be high [44]. A limitation of this study was that an important risk factor such as ulceration for melanoma survival was not documented in the cancer registries until January 2003. No information was available on treatment of patients,

but due to the lack of an effective treatment of advanced melanoma this should not have affected our results.

In conclusion, patients' demographics and classical melanoma characteristerics appear to be unable to explain the superior female survival after the diagnosis and progression of melanoma. Additional epidemiological and basic research is warranted to investigate this important gender difference in melanoma to improve prevention campaigns, medical management and possibly treatment. Future studies looking at factors influencing prognosis of melanoma patients should stratify their findings by sex.

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Figure legend

Figure 1: Crude survival by gender: results of the Kaplan-Meier analyses.
Black line: Kaplan-Meier curve for females, Grey line: Kaplan-Meier curve for males.
Circles: censoring events due to end of observation period or loss-to-follow-up.

Table 1. Studies concerning the prognosis of cutaneous MM, including >450 cases, that at least included breslow thickness and sex in the multivariate analysis.

				Confounders						Results	
References name and year of publication	Country	Total no. of patients	patients demographics	Breslow Thickness	Histologic subtype	Ulcera-tion	Tumor site	Level of invasion	Risk estimate	Risk estimate (95%CI) for females compared to males	
										Crude	Adjusted
Balch et al, 2001	USA	13,581[a]	Age, sex	+	-	+	+	+	RR		0.84 (0.76-0.92)
Schuchter et al, 1996	USA	488	Age, sex	+ *	+	-	+	+ *	OR		2.0 (1.2-3.6)†
Thorn et al, 1994	Sweden	498	Age, sex	+	-	-	-	-	HR		0.77
Ringborg et al, 1993	Sweden	581[b]	sex	+	+	-	+	-	HR	0.5 (0.4-0.8)	0.7 (0.5-1.0)
Masback et al,2001	Sweden	711	Age, sex	+	+ **	+	+	-	OR		0.9 (0.8-1.0)
Fortes et al, 2006	Italy	1012	Age, sex	+	+	+	-	-	RR		0.65 (0.34-1.23)
Karjalainen,1988	Finland	4980	sex	+	-	-	+	-	RR		0.67 (0.57-0.8)‡
Downing et al,2006	England	5513	age,sex, SES	+	+	-	-	-	HR	0.57 (0.48-0.67)	0.67 (0.56-0.80)

Abbreviations; OR (Odds Ratio), RR (Relative Risk), HR (Hazard Ratio), CI (Confidence Interval), SES (socioeconomic status)

[a] estimates for patients without evidence of nodal or distant metastases

b estimates for patients with a head and neck melanoma only

*not statistically significant in multivariate analysis

**for nodular MM only

† 10yr OR for remaining alive for female

‡ for 6th-10th yr of follow-up

Table 2: Sex-specific distribution of melanoma characteristics

Variable		Males (N)	%	Females (N)	%	p-value[#]
Age	Mean (years)	55.29 (4430)		53.18 (6108)		<0.0001
Histology	SSM	2128	48.0	3304	54.1	0.007
	LMM	140	3.1	214	3.5	
	NM	750	16.9	716	11.7	
	ALM	30	0.7	52	0.9	
	Other	1382	31.2	1822	30	
Site	Upper limbs	679	15.3	1228	20.1	<0.0001
	Lower limbs	736	16.6	2431	39.8	
	Head & neck	741	16.7	699	11.4	
	Trunk	2022	45.6	1546	25.3	
	Other & NOS	252	5.7	204	3.3	
TNM-N	TNM-N0/X	4156	93.8	5890	96.4	<0.0001
	TNM-N1+	274	6.2	200	3.3	
TNM-M	TNM-M0/X	4380	98.9	6080	99.5	<0.0001
	TNM-M1	50	1.1	28	0.5	
Breslow thickness	<1.00 mm	1797	40.6	3138	51.4	<0.0001
	1.0-2.0	952	21.5	1281	21.0	
	2.0-4.0	710	16.0	707	11.6	
	>4.0	532	12.0	465	7.6	
	Missing information	439	9.9	517	8.5	
Ulceration*	Present	61	18.9	54	12	0.42
	Absent	198	61.5	325	72	
	Missing information	63	19.6	72	16	

[#] Mantel-Haenzel Chi-squared test
* Only available for patients diagnosed in 2003-2004
TNM-N: nodal status
TNM-M: metastatic status

Table 3: results of univariate and multivariate analyses (total N=10,538).

Variable		Univariate RER	95% CI	Adjusted RER	95% CI$
Sex	Female	1.0		1.0	
	Male	2.70	2.38-3.06	1.87	1.65-2.10
Region*	IKZ	1.0		1.0	
	IKA	0.84	0.73-0.97	0.91	0.79-1.05
	IKN	0.94	0.80-1.10	0.77	0.66-0.89
Agegroup	0-44	1.0		1.0	
	45-54	1.24	1.06-1.45	1.21	1.03-1.41
	55-64	1.64	1.39-1.93	1.33	1.14-1.57
	65-74	1.87	1.55-2.25	1.37	1.15-1.64
	75-84	2.92	2.35-3.63	2.20	1.80-2.70
	≥ 85	4.44	2.87-6.87	2.18	1.39-3.40
Histology	SSM	1.0		1.0	
	LMM	0.12	0.002-10.1	0.39	0.12-1.33
	NM	5.11	4.31-6.05	1.53	1.29-1.81
	ALM	2.38	1.17-4.87	1.47	0.78-2.79
	Other	3.83	3.24-4.42	1.73	1.50-2.02
Site	Head & neck	1.0		1.0	
	Upper limbs	0.62	0.48-0.80	0.84	0.67-1.05
	Lower limbs	0.55	0.43-0.69	0.88	0.71-1.09
	Trunk	1.00	0.81-1.23	1.22	1.01-1.47
	Other & NOS	7.77	6.23-9.69	8.28	6.48-10.6
TNM-N	N0/NX	1.0		1.0	
	N1+	5.93	4.58-7.67	9.20	5.40-15.7
TNM-M	M0/MX	1.0		1.0	
	M1	24.77	19.06-32.2	11.17	8.19-15.2
Breslow	<1.00 mm	1.0		1.0	
Thickness	1.0-2.0	0.49	0.26-0.92	1.76	1.42-2.18
	2.0-4.0	1.19	0.71-1.97	4.18	3.42-5.12
	>4.0	1.86	1.13-3.06	6.39	5.18-7.89
	Missing	1.81	1.02-3.23	2.43	1.95-3.05
TNM-N* TNM-M	N1*M1	-		0.43	0.23-0.78
TNM-N * Breslow	N1* Bres X	-		0.52	0.25-1.07
	N1* > 4 mm	-		0.23	0.13-0.42
	N1* 2-4 mm	-		0.31	0.17-0.57
	N1* 1-2 mm	-		0.31	0.15-0.64

* Region = comprehensive cancer centre
TNM-N: nodal status determined by pathologist: N0: no nodal involvement, N1+: 1 or more lymph node involved, TNM-M: metastatic spread: M0: no metastatic spread, M1: presence of distant metastases

Table 4: results multivariate analyses for patients diagnosed in 2003-2004, with information on ulceration (N=773).

Variable		Adjusted RER	95% CI
Sex	Female	1.0	
	Male	1.51	0.59-3.86
Age	1-year increment	1.01	0.98-1.04
Nodal Status	N0	1.0	
	N1+	3.43	1.42-8.31
Metastatic Status	M0	1.0	
	M1	6.88	1.67-28.2
Breslow thickness	<1.00 mm	1.0	
	1.0-2.0	2.13	0.23-19.6
	2.0-4.0	3.94	0.50-31.0
	>4.0	4.99	0.64-39.1
	Missing information	6.48	0.88-47.7
Ulceration	Absent	1.0	
	Present	3.06	1.13-8.25
	Missing information	1.29	0.37-4.58

Table 5. relative excess risk (RER) estimates of dying for female versus male melanoma patients according to number of years of follow-up

Years after diagnosis	Nr of deaths	Univariate RER females vs males	95% CI	Adjusted RER Females vs males*	95% CI
0-1	588	2.55	1.98-3.28	1.63	1.29-2.08
1-2	525	2.54	1.95-3.31	1.68	1.30-2.18
2-3	426	3.25	2.41-4.39	2.15	1.60-2.89
3-4	306	2.80	1.96-4.00	1.90	1.32-2.74
4-5	234	2.97	1.90-4.65	2.42	1.48-3.98
5-6	170	1.69	0.95-2.98	1.26	0.71-2.24
>6	328	2.02	1.28-3.17	1.48	0.94-2.33

* Corrected for sex, region, agegroup, histology, site, nodal status, metastatic status, breslow thickness