A population-based registry study on relative survival from melanoma in Germany stratified by tumor thickness for each histologic subtype

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Background: Differences in relative survival (RS) of melanoma between histologic subtypes were discussed to be mainly caused by tumor thickness.

Objective: To investigate RS of melanoma, stratified by tumor thickness for each histologic subtype, and identify survival trends.

Methods: With use of cancer registry data on melanoma cases (*International Classification of Diseases, 10th Revision*, codes C43.0–C43.9) diagnosed in Germany in 1997–2013, 5- and 10-year age-standardized RS stratified by histologic subtype and stratified or standardized by T stage was estimated by standard and modeled period analyses. We restricted 10-year RS analyses to patients younger than 75 years.

Results: We analyzed 82,901 cases. Overall, the 5- and 10-year RS rates were 91.7% and 90.8%, respectively. Prognosis worsened with increasing T stage for all histologic subtypes, but T-stage distribution varied substantially. Survival differences by histologic subtype were strongly alleviated after adjustment for T stage but remained significant. Overall, 5-year RS increased significantly (by 3.8 percentage points) between the periods 2002–2005 and 2010–2013. This increase was no longer seen after adjustment for T stage.

Limitations: Exclusion of cases on account of missing information on T stages, changes in the definition of T stages, and lack of information on screening and treatment limit our analyses.

Conclusion: Differences in RS between histologic subtypes were strongly mediated by tumor thickness. Over time, RS of melanoma increased as a result of changes in T-stage distribution. (J Am Acad Dermatol 2019;80:938-46.)

Key words: histologic subtype; histology; melanoma; prognosis; prognostic factor; relative survival; stage; T stage; trend; tumor thickness.

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Funding sources: Supported by German Cancer Aid (Deutsche Krebshilfe) (grants 10825 and 110446).

Conflicts of interest: None disclosed.

The study outline was presented in a poster presentation at the annual conference of the German Society for Epidemiology in Munich, Germany, on September 2, 2016. Recent trends in relative survival of melanoma in Germany stratified by age group, T stage, and histologic subtype were presented at the annual conference of the German Society for Epidemiology in Lübeck, Germany, on September 7, 2017, and at the annual conference of the International Association of Cancer Registries in Utrecht, The Netherlands, on October 17, 2017.

Accepted for publication September 7, 2018.

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Published online September 20, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.09.018

Worldwide, nearly 55,500 deaths from melanoma occurred in 2012.[1] In Germany, about 2900 patients died of melanoma.[2] Age-standardized mortality per 100,000 (old European standard population) was 1.7 for women and 3.0 for men.[2] In 2008, a nationwide skin cancer screening program was implemented in Germany.[3] Novel immunotherapies and targeted therapies such as ipilimumab and vemurafenib were authorized in 2011[4] and 2012,[5] respectively. In 2014, melanoma was newly diagnosed in 16.6 women and 18.9 men per 100,000 in Germany (age-standardized incidence with the old European standard population).[2]

The most frequent histologic subtype is superficial spreading melanoma (SSM), followed by nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). Other rarer histologic subtypes account for the remainder of the diagnoses.[6,7] Growth of melanoma varies by histologic subtype. SSM grow laterally before vertical infiltration develops, whereas NM is the most aggressive type, growing rapidly.[8,9] Though prognosis is good overall, relative survival (RS) for certain histologic subtypes and advanced stages is low.[6] Differences in RS according to histologic subtype were previously discussed to be mediated by tumor thickness.[8,10,11]

However, little is known about the stage-standardized RS differences between histologic subtypes or the stage-specific RS stratified by histologic subtype. These estimates are important because of the controversies surrounding the benefits of screening, particularly if earlier diagnosis of SSM (which usually has a good prognosis) could have an impact on melanoma mortality.[12,13] Thus, whether thick SSMs also have a poor prognosis has to be examined. Furthermore, the extent to which the overall high RS for SSM and LMM and the low RS for NM and ALM result from differences in stage distributions needs to be assessed.[6]

Therefore, the aim of this study was to estimate 5- and 10-year RS stratified by T stage for each histologic subtype. Furthermore, we sought to identify recent trends in prognosis and compare histologic subtypes with and without standardization for T stage.

CAPSULE SUMMARY

- Relative survival of melanoma varies by histologic subtype. However, differences were strongly alleviated after adjustment for tumor thickness.
- Increased 5-year relative survival between the periods 2002–2005 and 2010–2013 is explained by a decrease in tumor thickness. Prevention and awareness should be encouraged, as the prognosis of thick melanoma is still poor.

METHODS

Database

This population-based study used routinely collected observational data from 12 cancer registries that were provided by the Cancer Survival Working Group of the Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Network of Epidemiologic Cancer Registries in Germany).[14] Cancer registries were selected on the basis of the quality of their data regarding the proportion of death certificate–only (DCO) cases. Methods and quality requirements have been outlined in detail before.[14] Our data set covers a population of 28.2 million inhabitants of Germany (34.9%). We included more than 80,000 patients age 15 years or older with a primary cutaneous malignant melanoma (*International Classification of Diseases, 10th Revision* (ICD-10), codes C43.0–C43.9) that was diagnosed in 1997–2013. DCO cases were excluded. Survival analyses were stratified by tumor thickness operationalized in accordance with the tumor, node, and metastasis (TNM) staging system[15] as T0, T1, T2, T3, T4, and TX (cases with unknown or missing tumor thickness) and by histologic subtype. The histologic subtypes SSM, NM, LMM, ALM, and "other" (including amelanotic melanoma, malignant melanoma in junctional nevus, desmoplastic melanoma, and spindle cell melanoma) were analyzed.

Statistical methods

To quantify the excess mortality due to melanoma we estimated RS as the ratio of the observed survival rate in patients with melanoma and the expected survival rates in the general population.[16,17] RS estimates higher than 100% were possible and indicate—if incomplete registration of deaths is not an issue—higher survival rates in patients than in the general population.[18] Using population life tables stratified by age, sex, and calendar year, we calculated the expected numbers of deaths according to the Ederer II method.[19] The 5- and 10-year RS rates were estimated by conventional and model-based period analysis.[20,21] All survival estimates were age-standardized according to the International Cancer Survival Standards.[22]

For comparison of histologic subtypes, we calculated RS adjusted for age and T stage by model-based period analysis. The distribution of stages T1 to T4 in the whole data set was used as a standard for weighting T stages in the histologic subtype groups. Cases with T0 melanoma or

Abbreviations used:

ALM: acral lentiginous melanoma
DCO: death certificate only
LMM: lentigo maligna melanoma
NM: nodular melanoma
RS: relative survival
SE: standard error
SSM: superficial spreading melanoma
TNM: tumor node and metastasis

unknown tumor thickness were excluded from all T-stage–adjusted analyses. Statistical significance of differences in RS between histologic subtypes was tested with SSM as a reference category. For this model-based histologic comparison, the number of excess deaths was modeled as a function of year of follow-up, age group, and T stage by Poisson regression with the logarithm of the person-years at risk as offset. Trends in 5-year RS by histologic subtype were examined with and without adjustment for T stage for the periods 2002–2005, 2006–2009, and 2010–2013 from January to December, respectively. For this trend analysis, we included the factor calendar period in the model instead of T stage as compared with in the model described earlier. For the T-stage–adjusted trend analyses, we used the distribution of T stages in the first period 2002–2005 as a standard. In sensitivity analyses, we assessed the effect of excluding cases involving patients age 75 years or older. The 10-year RS analyses were restricted to cases of patients with melanoma who were younger than 75 years at diagnosis to prevent potential biases due to a suspected incomplete registration of deaths and a higher proportion of DCO cases in this age group.

The SAS statistical software package (version 9.2, SAS Institute Inc, Cary, NC) was used, and we applied the SAS marco period[23] to carry out conventional period analysis.[20,24] A significance level of 0.05 was used in 2-sided testing for statistical significance. We did not report RS when estimates were too imprecise (standard error [SE] >5.0%).

RESULTS

In total, we included 82,901 melanoma cases with a balanced sex ratio (51.0% women) and a median patient age of 62 years at diagnosis (Table I). Median age at diagnosis ranged between 58 and 64 years in the different regions. The percentage of histologically confirmed cancer diagnosis was greater than 98.7% in all registries and was 99.6% overall. In 2002–2013, the percentage of excluded DCO cases was 2.2%. All together, 16,335 patients (19.7%) had melanoma of stage T0 or with an unknown or missing tumor thickness (TX).

Five-year RS

The age-standardized 5-year RS for the period 2002–2013 was 91.7% (SE, 0.2%) overall. As shown in Table II, RS differed by histologic subtype. Survival of patients with SSM (99.7% [SE, 0.2%]) and LMM (100.9% [SE, 0.5%]) was similar to that of the general population. NM (76.9% [SE, 0.6%]), ALM (83.4% [SE, 1.4%]), and melanoma of other histologic subtypes (84.5% [SE, 0.3%]) were associated with a lower RS. In all histologic subtypes, prognosis worsened with increasing T stage. The strongest gradients were observed for LMM and other melanoma, with the RS of both being 48 percentage points lower in stage T4 than in stage T1. Distribution of T stages differed substantially. The proportion of advanced melanoma of stage T3 or T4 was low in SSM (9.2%) and LMM (8.2%). In contrast, NM (67.6%), ALM (49.4%), and other melanoma (28.1%) were diagnosed at stage T3 or T4 more frequently.

Ten-year RS

Overall, the 10-year RS of patients with melanoma who were younger than 75 years at diagnosis was 90.8% (SE, 0.3%) in the period 2007–2013 (Table III). When 16,239 cases involving patients 75 years or older (20%) were excluded, the overall 10-year RS decreased by 1.2 percentage points (data not shown). Exclusion of cases involving patients 75 years or older especially decreased the RS of patients with SSM and LMM and the RS of patients with T1-melanoma of all histologic subtypes. Compared with the 5-year RS, the 10-year RS of cases involving patients younger than 75 years differed even slightly more clearly between the histologic subtypes (by up to 27.3 percentage points [LMM vs NM]) (Table III). The decline of 10-year RS with increasing tumor thickness from stage T1 to T4 was more pronounced than was the decline of 5-year RS. This decline was strongest in other melanoma (60.9 percentage points).

Comparison of histologic subtypes

As a result of standardization for age and T stage, the differences in 5-year RS between the histologic subtypes diminished from a range between 77.3% (SE, 0.6%) and 100.5% (SE, 0.5%) to a range between 89.5% (SE, 0.8%) and 95.3% (SE, 0.4%) (Table IV). However, some differences remained, and the difference between SSM as a reference compared with NM, ALM, and other melanoma was statistically significant in the model-based histologic

Table I. Characteristics of melanoma cases (ICD-10 codes C43.0–C43.9) diagnosed in Germany, 1997–2013

Federal state registry	Calendar years with available data	Population covered in 2013, million	Covered proportion of population, %	Cases, n (%)*	Sex, % female*	Median age, y*	Histologically confirmed, %*	Death certificate only, %†
Brandenburg	1997-2013	2.45	100.0	6275 (7.6)	48.7	63	99.7	1.4
Bremen	1998-2013	0.66	100.0	1859 (2.2)	50.2	64	99.7	1.8
Hamburg	1997-2013	1.75	100.0	5340 (6.4)	52.2	63	99.9	3.1
Mecklenburg-Western Pomerania	1997-2013	1.60	100.0	4292 (5.2)	52.5	63	99.8	1.6
Lower Saxony	2003-2013	7.79	100.0	21,653 (26.1)	52.1	62	98.7	2.8
North Rhine-Westphalia‡	1997-2013	2.57	14.6	7837 (9.5)	54.0	58	99.7	1.6
Rhineland-Palatinate‡	1998-2013	2.16	54.1	7696 (9.3)	50.6	61	99.9	1.4
Saarland	1997-2013	0.99	100.0	2961 (3.6)	49.6	62	99.8	1.4
Saxony	1997-2013	4.05	100.0	11,964 (14.4)	48.2	64	99.8	1.2
Saxony-Anhalt‡	1997-2013	0.67	29.8	1856 (2.2)	51.2	64	99.8	1.8
Schleswig-Holstein‡	1999-2013	1.35	48.0	4843 (5.8)	52.5	61	100.0	4.8
Thuringia	1997-2013	2.16	100.0	6325 (7.6)	49.7	61	99.9	1.8
Total	—	28.20	35.0	82,901 (100.0)	51.0	62	99.6	2.2

ICD-10, International Classification of Diseases, 10th Revision.
*Excluding DCO cases.
†In 2002–2013.
‡Administrative areas with a low proportion of death certificate only cases were selected.

comparison with adjustment for age and T stage (all $P < .05$).

Trends in prognosis

Age-standardized 5-year RS improved significantly from 89.6% (SE, 0.4%) in 2002–2005 to 93.4% (SE, 0.2%) in 2010–2013 ($P < .001$ [data not shown]) (Fig 1). With stratification by histologic subtype, significant improvements were seen only for patients with other melanoma: from 82.0% (SE, 0.7%) to 87.1% (SE, 0.5%) ($P < .001$). In the trend analysis adjusted for age and T stage, prognosis worsened overall (−0.5 percentage points [$P = .032$]), with the 5-year RS decreasing significantly for patients with SSM (−2.1 percentage points [$P < .001$]) and the trend in other melanoma disappearing.

Sensitivity analysis

Restricting analyses to cases involving patients younger than 75 years would have increased overall 5-year RS by 0.7 percentage points (data not shown).

DISCUSSION

This population-based registry study focused on the mediating effect of T stage on differences in RS between the histologic subtypes of melanoma. For all histologic subtypes, we found that patients with thicker tumors had a lower RS. Survival differences by histologic subtype were mediated largely, but not completely, by the T-stage distribution. The remaining differences may have been due either to distinct disease processes[25] or to residual confounding. Residual confounding could have occurred because the adjustment for age group and T stage was rather crude and the distribution of tumor thickness within the T stages and within the age groups may have differed further between the histologic subtypes. In some subgroups, survival rates were higher than in the general population, possibly because of the selection effects of screening or a bias toward healthy survivors (ie, change to a healthier lifestyle, intensified medical monitoring, etc).[26,27]

We found the prognosis of patients with melanoma in Germany to be quite similar to that in other Western countries.[28,29] In our study, age-standardized 5-year RS increased significantly in the decade examined. From a rate of 89.6% (SE, 0.4%) in the period 2002–2005, 5-year RS rose to 93.4% (SE, 0.2%) in 2010–2013. Prognosis was especially improved for patients with other melanoma (+5.1% [$P < .001$]). A previous study from Germany found no significant change in 5-year RS and only a slight decline for men, possibly because the investigated period of 2002–2006 was very short.[6] Prognosis also improved in other European countries, especially in Eastern Europe.[29-31] In the past, RS increased in the United States as well,[32] but not in Australia.[33]

To understand the changes in RS, some possible causes and also sources of confounding must be considered. The improvement in RS is strongly driven by a stage shift (ie, a shift over time to a

Table II. Age-standardized 5-year relative survival of melanoma cases (ICD-10 codes C43.0—C43.9) for the period 2002—2013 by T stage for each histologic subtype

Histologic subtype	n	(%)	RS	SE
Overall*	82,901		91.7	0.2
Superficial spreading (total)†	37,379		99.7	0.2
TX	4303	(11.5)‡	99.7	0.6
Superficial spreading with known stage	33,070	(100.0)		
T1	24,611	(74.4)	103.6	0.3
T2	5410	(16.4)	97.2	0.6
T3	2298	(6.9)	84.8	1.1
T4	751	(2.3)	57.2	2.7
Nodular (total)§	10,699		76.9	0.6
TX	957	(8.9)‡	72.8	2.0
Nodular with known stage	9739	(100.0)		
T1	1050	(10.8)	97.5	1.3
T2	2108	(21.6)	90.9	1.1
T3	3433	(35.3)	78.3	1.0
T4	3148	(32.3)	55.2	1.4
Lentigo maligna (total)‖	6942		100.9	0.5
TX	1167	(16.8)‡	103.2	0.7
Lentigo maligna with known stage	5770	(100.0)		
T1	4590	(79.5)	102.5	0.5
T2	705	(12.2)	98.2	1.4
T3	331	(5.7)	—¶	—¶
T4	144	(2.5)	54.3	4.5
Acral lentiginous (total)	1616		83.4	1.4
TX	184	(11.4)‡	82.5	3.8
Acral lentiginous with known stage	1432	(100.0)		
T1	427	(29.8)	97.7	2.0
T2	297	(20.7)	94.2	2.3
T3/T4	708	(49.4)	66.7	3.2
Other (total)#	26,233		84.5	0.3
TX	9511	(36.3)‡	74.4	0.6
Other with known stage	16,555	(100.0)		
T1	8747	(52.8)	101.7	0.5
T2	3154	(19.1)	94.9	0.8
T3	2490	(15.0)	80.4	1.2
T4	2164	(13.1)	53.4	1.7

ICD-10, International Classification of Diseases, 10th Revision; *RS*, point estimate of relative survival (%); *SE*, standard error (%); *TX*, cases with unknown or missing tumor thickness.

*Including cases with missing values in histologic subtype (n = 32 in 1997—2013).

†Excluding T0-superficial spreading melanoma (n = 6 in 1997—2013).

‡Percentage of the total number of cases with melanoma of the respective histologic subtype.

§Excluding T0-nodular melanoma (n = 3 in 1997—2013).

‖Excluding T0-lentigo maligna melanoma (n = 5 in 1997—2013).

¶Relative survival estimates with standard errors greater than 5.0% are not reported.

#Excluding T0-other melanoma (n = 167 in 1997—2013).

more favorable distribution of tumor thickness). This can be seen from the trend analyses that additionally adjust for T stage. With T-stage adjustment, the previously positive overall trend (+3.8 percentage points [$P < .001$]) turned into a significant negative trend (−0.5 percentage point [$P = .032$]). This decrease was seen especially for patients with SSM (−2.1 percentage points [$P < .001$]). The previously observed increase in age-standardized 5-year RS for patients with other melanoma vanished after adjustment for T stage. These trends suggest that implementation of the German nationwide skin cancer screening in 2008 mainly improved early detection of the generally slow-growing, less aggressive SSM and other melanoma, whereas more aggressive tumors with a poorer prognosis still tended to be diagnosed in later stages.

Effective screening should reduce the incidence of thick melanoma for all histologic subtypes. The possible impact of earlier diagnosis of SSM on

Table III. Age-standardized 10-year relative survival of patients with melanoma (ICD-10 codes C43.0–C43.9) younger than 75 years for the period 2007–2013 by T stage for each histologic subtype

Histologic subtype	n	(%)	RS	SE
Overall*	66,662		90.8	0.3
Superficial spreading (total)†	32,549		98.6	0.4
TX	3778	(11.6)‡	99.7	0.9
Superficial spreading with known stage	28,765	(100.0)		
T1	21,820	(75.9)	103.0	0.4
T2	4683	(16.3)	92.2	1.0
T3	1775	(6.2)	77.1	1.9
T4	487	(1.7)	45.1	4.1
Nodular (total)	7735		72.6	0.9
TX§	671	(8.7)‡	68.2	3.4
Nodular with known stage	7062	(100.0)		
T1	911	(12.9)	96.5	2.2
T2	1754	(24.8)	85.2	1.8
T3	2487	(35.2)	72.3	1.7
T4	1910	(27.0)	45.0	2.2
Lentigo maligna (total)	4159		99.9	1.0
TX	698	(16.8)‡	103.2	2.2
Lentigo maligna with known stage	3456	(100.0)		
T1	2897	(83.8)	101.4	1.0
T2	387	(11.2)	91.9	3.2
T3/T4	172	(5.0)	—‖	—‖
Acral lentiginous (total)	1129		76.1	2.4
TX¶	127	(11.2)‡	—‖	—‖
Acral lentiginous with known stage	1002	(100.0)		
T1/T2	557	(55.6)	89.5	3.3
T3/T4	445	(44.4)	53.2	4.7
Other (total)	21,073		83.7	0.5
TX#	7497	(35.6)‡	73.9	0.9
Other with known stage	13,439	(100.0)		
T1	7603	(56.6)	101.2	0.7
T2	2629	(19.6)	89.6	1.4
T3	1860	(13.8)	74.5	1.9
T4	1347	(10.0)	40.3	2.6

ICD-10, International Classification of Diseases, 10th Revision; *RS*, point estimate of relative survival (%); *SE*, standard error (%).
*Including cases with missing values in histology (n = 32 in 1997–2013).
†Excluding T0-superficial spreading melanoma (n = 6 in 1997–2013).
‡Percentage of the total number of cases with melanoma of the respective histologic subtype.
§Excluding T0-nodular melanoma (n = 3 in 1997–2013).
‖Relative survival estimates with standard errors greater than 5.0% are not reported.
¶Excluding T0-lentigo maligna melanoma (n = 5 in 1997–2013).
#Excluding T0-other melanoma (n = 167 in 1997–2013).

melanoma mortality might be limited though. The number of thick SSMs is already small, and whether a relevant reduction could be reached by screening is unclear. Moreover, screening could induce overdiagnosis and lead-time bias by increasing RS without significantly reducing mortality.[29] In addition, a more frequent classification of benign lesions as early-stage melanoma (ie, diagnostic drift) was previously discussed.[34] Therefore, the survival trends do not imply trends in melanoma mortality.

As we have already addressed, we found a shift to less thick tumors. This is a continuous phenomenon that is not restricted to a shift between T stages but also happens within T stages. In contrast to the stage shift between T stages, this within-stage shift cannot be adjusted for by T-stage standardization. Hence, smaller tumors increase the stage-specific RS. Consequently, the small negative trend in the model with adjustment for T stage could be expected to be actually stronger if the model were able to adjust completely for differences in the distribution of tumor thickness over time.

However, the negative trend should not be interpreted without considering that the TNM

Table IV. Five-year relative survival of melanoma cases (ICD-10 codes C43.0–C43.9) in Germany in the period 2002–2013 by histologic subtype standardized for age and standardized or adjusted for age and T stage

	Standardized for age				Standardized or adjusted for age and T stage			
Histologic subtype	**n**	**(%)**	**RS***	**SE**	**RS†**	**SE**	**Relative excess risk‡**	***P* value§**
Overall‖	66,566	(100.0)	93.7	0.2				
Superficial spreading	33,070	(49.7)	99.7	0.2	95.3	0.4	1 (reference)	
Nodular	9739	(14.6)	77.3	0.6	89.5	0.8	1.38	<.001¶
Lentigo maligna	5770	(8.7)	100.5	0.5	93.9	1.1	0.80#	.183
Acral lentiginous	1432	(2.2)	83.5	1.5	89.7	1.4	1.28	.013¶
Other	16,555	(24.9)	90.5	0.4	92.8	0.4	1.35	<.001¶

ICD-10, International Classification of Diseases, 10th Revision; *RS*, point estimate of relative survival (%); *SE*, standard error (%).
*Standardized for age.
†Standardized for age and T stage.
‡Relative excess risk was calculated by model-based period analysis and adjusted for age and T stage.
§Differences of relative survival estimates between each histologic subtype and superficial spreading melanoma as reference histologic subtype adjusted for age and T stage were tested by using model-based period analysis.
‖Excluding cases with T0-melanoma and unknown or missing T stage (TX) (n = 16335 in 1997–2013).
¶*P* values less than .05.
#The model-based estimate of relative survival for lentigo maligna melanoma was even larger than for superficial spreading melanoma but had a large variance.

classification changed from version 5 to version 6 in 2004, which was during the first period (2002–2005) of the trend analyses.[35,36] In TNM version 5, the stages T1, T2, and T3 comprised thinner tumors than in version 6 of the classification system. Thus, these tumors have been more advanced since implementation of TNM version 6. It can be suspected that the recently lower T-stage–adjusted RS is due not to worse treatment but rather to this artifact of a modified T-stage classification. On the contrary, novel drugs that enhance treatment of advanced melanoma have been approved in recent years. Our T-stage–adjusted trend analysis did not indicate first population-based effects of new treatments on overall RS. It is not possible to know whether this is due to an as-yet limited impact of the treatment or simply to data noise and difficulties in the incorporation of stage information.

Limitations and strengths

The main limitation of this study is the coarse resolution of tumor thickness. The use of T stage instead of a precise measurement of tumor thickness makes the analyses susceptible to problems such as residual confounding due to within-stage differences or confounding due to changes in TNM classification. Additionally, the T stage was missing or unknown for 16,154 patients with melanoma (19.5%). If these patients systematically differ from the other patients with regard to survival, our analyses will be not representative for the whole population of patients with melanoma. Further, the routinely collected data from cancer registries do not include sufficient information on covariates such as treatment, awareness, and self-examination, nor do they include information on screening participation. Thus, changes in those factors could not be considered explicitly in the trend analysis.

Despite these limitations, our study has several noteworthy strengths. The large representative data set facilitated stratification of age-standardized RS by both histologic subtype and T stage, and it allowed adjustment for age and T stage in trend analysis. High-quality, population-level data starting in 1997 and reflecting long follow-up were used. For evaluation of the most recent survival estimates, we conducted both conventional and model-based period analysis. To avoid overestimation of long-term RS because of a suspected incomplete mortality follow-up, we excluded cases involving patients 75 years or older from the 10-year RS analysis.

In conclusion, our study indicated that patients with thick melanoma had a low RS irrespective of histologic subtype. Differences in RS between histologic subtypes seemed to result mostly from differences in stage distributions. RS of melanoma increased significantly due to a more favorable stage distribution. Screening most likely achieved this stage shift by allowing earlier diagnosis of SSM. Because overdiagnosis, lead-time bias, and diagnostic drift[34] cannot be ruled out, this increase in RS does not imply that mortality was also reduced. Hence, there is considerable uncertainty regarding how far prognosis of patients with melanoma truly improved. Therefore, trends of population-based stage-specific incidence and mortality stratified by histologic subtype need to be additionally

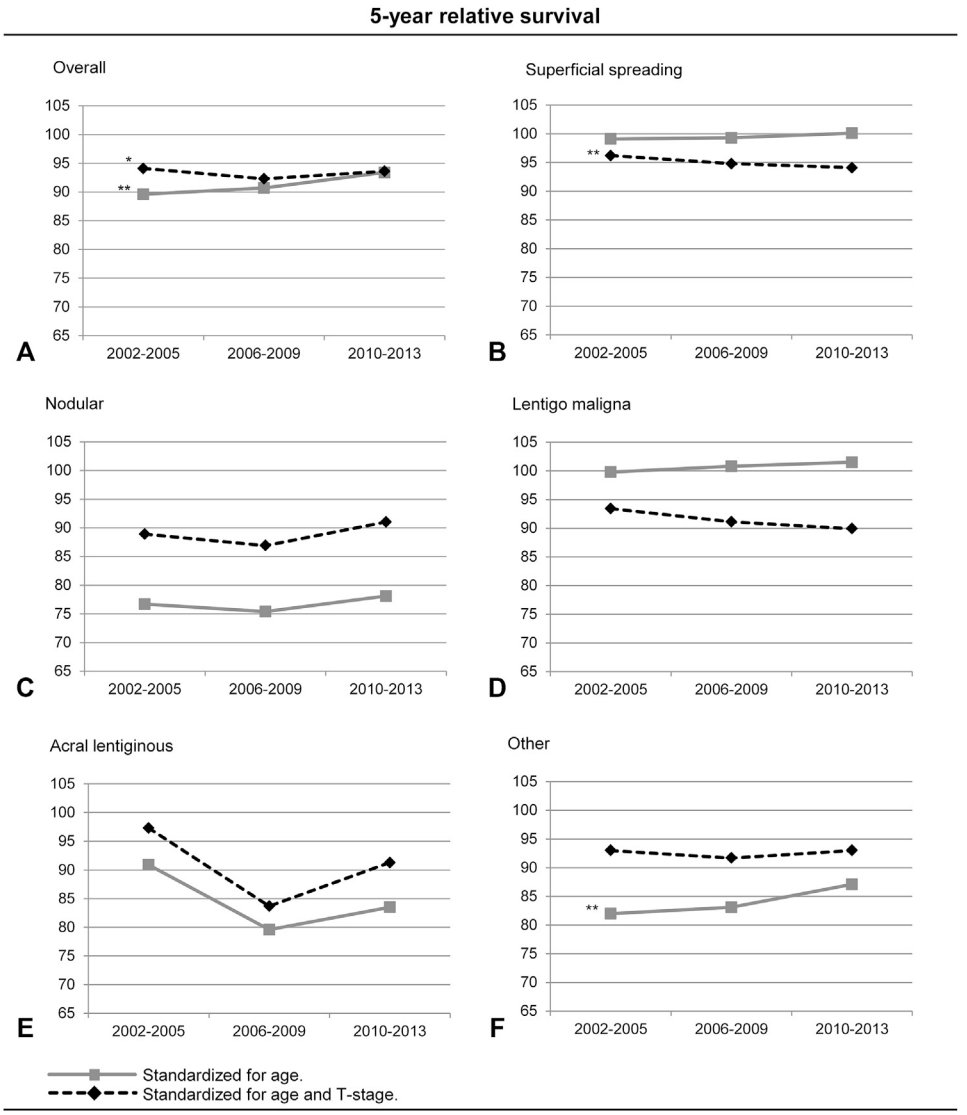

Fig 1. Analysis of trends in age-standardized 5-year relative survival of patients with melanoma (*International Classification of Diseases, 10th Revision,* code C43.0-C43.9) in Germany between the periods 2002−2005, 2006−2009, and 2010−2013 overall (**A**) and by histologic subtype (**B** to **F**) with and without standardization for T stage. (Statistically significant trends are designated with one asterisk for *P* less than .05 and two asterisks for *P* less than .001.)

investigated in future research. Screening participation and use of novel treatments should therefore be considered. Because the prognosis of thick melanoma is still poor, prevention and awareness should be encouraged.

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REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [online].* Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr/Pages/summary_table_site_sel.aspx. Accessed July 23, 2018.
2. *Association of Population-Based Cancer Registries in Germany. GEKID atlas*; 2016. Available at: http://www.gekid.de/. Accessed July 23, 2018.
3. Krebsfrüherkennungs-Richtlinien. *Bundesanzeiger AT 31.12.2014 B4*. Germany: German Federal Gazette; 2014. Available at:

https://www.g-ba.de/downloads/62-492-950/KFE-RL_2014-07-24.pdf. Accessed July 23, 2018.

4. European Medicines Agency. *Summary of Product Characteristics*. Yervoy Ipilimumab; 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf. Accessed July 23, 2018.
5. European Medicines Agency. *European public assessment report (EPAR) Summary for the Public. Zelboraf vemurafenib. EMA/53181/2012 EMEA/H/C/002409. London, United Kingdom*; 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002409/WC500124320.pdf. Accessed July 23, 2018.
6. Eisemann N, Jansen L, Holleczek B, et al. Up-to-date results on survival of patients with melanoma in Germany. *Br J Dermatol*. 2012;167:606-612.
7. Barnes B, Kraywinkel K, Nowossadeck E, et al. *Report on Cancer in Germany, 2016*. [in German]. Berlin: Robert Koch Institute; 2016:53-56.
8. LeBoit PE, Burg G, Weedon D, et al. *World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours*. Lyon: IARC Press; 2006.
9. Liu W, Dowling JP, Murray WK, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Arch Dermatol*. 2006;142:1551-1558.
10. Koh HK, Michalik E, Sober AJ, et al. Lentigo maligna melanoma has no better prognosis than other types of melanoma. *J Clin Oncol*. 1984;2:994-1001.
11. Cox NH, Aitchison TC, Sirel JM, MacKie RM. Comparison between lentigo maligna melanoma and other histogenetic types of malignant melanoma of the head and neck. Scottish Melanoma Group. *Br J Cancer*. 1996;73:940-944.
12. Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. *J Am Acad Dermatol*. 2012;66:201-211.
13. Conic RZ, Cabrera CI, Khorana AA, Gastman BR. Determination of the impact of melanoma surgical timing on survival using the National Cancer Database. *J Am Acad Dermatol*. 2018;78:40-46.e7.
14. Jansen L, Castro FA, Gondos A, et al. Recent cancer survival in Germany: an analysis of common and less common cancers. *Int J Cancer*. 2015;136:2649-2658.
15. Union for International Cancer Control (UICC). *TNM classification of malignant tumours; publications and resources*; 2017. Available at: https://www.uicc.org/resources/tnm/publications-resources. Accessed July 23, 2018.
16. Brenner H, Hakulinen T. Implications of incomplete registration of deaths on long-term survival estimates from population-based cancer registries. *Int J Cancer*. 2009;125:432-437.
17. Henson DE, Ries LA. The relative survival rate. *Cancer*. 1995;76:1687-1688.
18. Brenner H, Arndt V. Long-term survival rates of patients with prostate cancer in the prostate-specific antigen screening era: population-based estimates for the year 2000 by period analysis. *J Clin Oncol*. 2005;23:441-447.
19. Ederer F, Heise H. *Instructions to IBM 650 Programmers in Processing Survival Computations*. Bethesda, MD: National Cancer Institute; 1959.
20. Brenner H, Hakulinen T. Up-to-date and precise estimates of cancer patient survival: model-based period analysis. *Am J Epidemiol*. 2006;164:689-696.
21. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer*. 1996;78:2004-2010.
22. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40:2307-2316.
23. Brenner H, Gefeller O, Hakulinen T, Arndt V. *SAS Macro Period and Sas Macro Periodh: Period Analysis of Survival Data*; 2004. Available at: http://www.imbe.med.uni-erlangen.de/cms/software_period.html. Accessed July 23, 2018.
24. Brenner H, Gefeller O, Hakulinen T. A computer program for period analysis of cancer patient survival. *Eur J Cancer*. 2002;38:690-695.
25. Cockburn M, Peng D, Key C. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. In: Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, eds. Bethesda, MD: National Cancer Institute, SEER Program; 2007:93-100.
26. Koh HK, Lew RA, Prout MN. Screening for melanoma/skin cancer: theoretic and practical considerations. *J Am Acad Dermatol*. 1989;20:159-172.
27. Humpel N, Magee C, Jones SC. The impact of a cancer diagnosis on the health behaviors of cancer survivors and their family and friends. *Support Care Cancer*. 2007;15:621-630.
28. Howlader N, Noone AM, Krapcho M, et al. *SEER cancer statistics review, 1975-2013*. Bethesda, MD: National Cancer Institute; 2016. Available at: https://seer.cancer.gov/archive/csr/1975_2013/. Accessed July 23, 2018.
29. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. *Lancet Oncol*. 2014;15:23-34.
30. Gondos A, Bray F, Hakulinen T, et al. EUNICE Survival Working Group. Trends in cancer survival in 11 European populations from 1990 to 2009: a model-based analysis. *Ann Oncol*. 2009;20:564-573.
31. Galceran J, Uhry Z, Marcos-Gragera R, et al. Trends in net survival from skin malignant melanoma in six European Latin countries: results from the SUDCAN population-based study. *Eur J Cancer Prev*. 2017;26:S77-S84.
32. Shaikh WR, Dusza SW, Weinstock MA, et al. Melanoma thickness and survival trends in the United States, 1989 to 2009. *J Natl Cancer Inst*. 2016:108.
33. Downing A, Yu XQ, Newton-Bishop J, et al. Trends in prognostic factors and survival from cutaneous melanoma in Yorkshire, UK and New South Wales, Australia between 1993 and 2003. *Int J Cancer*. 2008;123:861-866.
34. Levell NJ, Beattie CC, Shuster S, Greenberg DC. Melanoma epidemic: a midsummer night's dream? *Br J Dermatol*. 2009;161:630-634.
35. Wittekind C, Wagner G. *TNM Classification of Malignant Tumours*. [in German]. 5th ed. Berlin, Heidelberg, New York: Springer; 1997.
36. Wittekind C, Meyer HJ, Bootz F. *TNM Classification of Malignant Tumours*. [in German]. 6th ed. Heidelberg, New York: Springer; 2002.